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MERCURY POISONING.

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The evaluation through clinical results of any measures employed for the treatment of mercury poisoning is extremely difficult, chiefly because estimation of the effective doses of mercury is almost impossible. In all series of cases recoveries are reported after enormous doses, death after comparatively trivial amounts of the drug. In dogs Sansum[27] found that 4 mg. of the bichlorid given intravenously proved almost regularly fatal, although it did not produce anuria; 5 mg. per kilo invariably caused anuria and death. Such doses, equivalent to only 0.28 to 0.35 gm. for a 70-kilo human are far smaller than those which have proved lethal in clinical studies of poisoning. Haskell, Carder and Coffindaffer[10] administered the drug in solution by stomach tube to dogs who had received an injection of morphin to allay the tendency to vomit. Under these circumstances they found that a dose of 20 mg. per kilo was invariably fatal. The extraordinary difference in magnitude between the intravenous and peroral minimal lethal doses can be ascribed to incomplete or retarded absorption from the alimentary canal. If the tolerance of humans is similar to that of dogs, it would be a reasonable expectation that a 70-kilo adult would survive if he took and retained less than 1.4 gm. of the drug. In

other words, recovery after the ingestion of less than 3 of the common 7.5-grain tablets should be considered imperfect evidence of therapeutic success. This conclusion is in accord with most clinical reports, including the series of cases which will be presented below.[1,9,29]

The situation is still further complicated in human cases by the early institution of measures to prevent absorption and to recover the drug from the stomach before it can be absorbed. The outcome of bichlorid poisoning is largely dependent upon the interval which elapses between the ingestion of the mercury and the institution of emetic measures and gastric lavage.[1,9,29]

It is not entirely possible to resolve these doubts by quantitative analysis of the excreta. The analytical difficulties involved in the quantitative recovery of mercury from the enormous mass of fluids used for lavage or excreted in diarrhea and vomiting are considerable. Early vomitus, urine, stools and lavage fluids are invariably incompletely preserved. Moreover, in the initial stages, at least, it is hard to know whether to count mercury recovered from the bowel and stomach as part of the effective dose or merely unabsorbed material.

For all these reasons mortality statistics afford an extremely uncertain criterion of the value of any therapeutic measures. Certain data on the cases treated in the New Haven Hospital, from 1922 to the present, are, however, worthy of mention.

In all, there have been 37 patients who presumably took mercury in the form of bichlorid tablets. One of these is supposed to have attempted suicide by this means twice. Of the 37, 28 survived, 9 died, a mortality of approximately 25 per cent. Of the survivors, in spite of history and circumstantial evidence, there is some uncertainty whether 4 patients took or absorbed any significant amount of poison. Cases have been omitted whose histories of poisoning seem entirely unreliable. As far as the relation of dosage of mercury and initial treatment to mortality is concerned, the results in this series differ little from those reported by other observers. No patient who had received less than 3 tablets of bichlorid (1.5 gm.) died; none who had taken more than 4 tablets survived. Of the 6 who survived after taking 3 or 4 tablets, 1 spit out 2 of the 3 tablets unswallowed; 1 was reported to have taken 4 tablets in solution, but no mercury was found in his urine. One other survivor is known to have taken more than 1 tablet, but the actual amount taken is uncertain. Of the 9 who died 4 only took 3 or 4 tablets.

Of the survivors, 17 vomited at once, and all those who took 2 or more tablets vomited within 20 minutes. Of the fatal cases, 3 with doses of 3, 5 and 7 tablets, respectively, vomited within 20 minutes; the time of vomiting in 4 cases could not be ascertained. Sixteen survivors received gastric lavage within 30 minutes, and of

these all who took more than 2 tablets were either lavaged or treated very soon after taking the poison. Of the fatal cases only 2, with 3 and 5 tablets, respectively, received early treatment or lavage.

Twelve, 2 of whom took more than 2 tablets, recovered without parenteral administration of fluids; 13 survivors, of whom 3 took more than 2 tablets, were given parenteral fluids. Of the 9 who died, 1, with 5 tablets, received a hypodermoclysis after 1 hour; 2 were given hypodermoclyses or infusions after 4 or more hours, the others only after intervals varying from 7 hours to 8 days.

The conclusions that can be drawn are that the mortality in bichlorid poisoning depends chiefly upon the amount of the drug taken and absorbed.

The relation of mortality to the symptoms which the patients developed differs, perhaps, in some respects, from other reported series. Among the survivors, with the exception of 2, there is almost complete absence of important symptoms. None had even transitory anuria and only 2 developed significant morphologic urinary changes; 2 had transitory diarrhea, 1 with bloody stools; 4 vomited for 24 hours, but not enough to impair their urinary output, and of these 1 was highly alcoholic, another had chronic gastritis and a third had renal colic; 1 developed a definite mercurial stomatitis. On the other hand, of the fatal cases, all developed diarrhea, vomiting and anuria early, and all but 1 had stomatitis. Two survivors, Cases 44720 and A-6100, who have been omitted from the statistical treatment will be discussed in detail later.

Because of the complete absence of symptoms among survivors it might appear either that the therapeutic measures employed in these cases were peculiarly efficacious in aborting symptoms, but of no ultimate life-saving value; or that the treatments given were of no value and those that survived had not received toxic doses of the poison. It is, however, possible to adopt an entirely different point of view, concluding that mortality statistics are of little value as criteria of therapeutic methods. There are such obvious distinctions between the fatal and nonfatal cases that statistical treatment is inapplicable, because it involves comparison of incomparables. This is, however, the method which has been generally employed for the evaluation of procedures for the treatment of mercury poisoning. It should be possible to find more valid criteria in a study of the responses of functional disturbances and symptoms to therapeutic measures.

Any such analysis must depend upon a clear understanding of the action of mercury and the manner in which it produces its fatal effect. The distribution of the pathologic lesions which result from mercury is remarkably constant, regardless of the route by which the drug is administered; the intensity of the effect in various organs depends upon the mode of administration. In all cases one finds necrosis of the epithelium of the alimentary canal and the tubular

epithelium of the kidneys, with minor changes in other organs, especially the liver, presumably points at which the mercury accumulates in high concentration during the processes of absorption or excretion. The alimentary tract, and particularly the stomach, suffers more intensely when the poison is taken perorally.[16] There is little doubt that mercury is excreted into the stomach,[19] and by the intestine, liver and kidneys.[14,25] However, after ingestion of the drug, alimentary tract lesions are probably due to damage produced by the drug before it is absorbed or even by that which is never absorbed, and occur chiefly during the initial hours when the gastric and intestinal walls are exposed to maximum concentrations of the metal.

Sublethal doses of mercury cause profuse diuresis,[14,25,27] probably by producing a large glomerular filtrate. Even lethal doses, which result in anuria, do not appear to disturb glomerular function greatly, and may even accelerate filtration.[25] Such doses do, however, cause necrosis of the renal tubular epithelium, perhaps, as has been suggested, because the poison is concentrated by the process of reabsorption in the tubules.[13,24] In diuresis produced by mercurials, it has been shown by Keith and Whelan,[14] the majority of the mercury is excreted promptly in the urine. Even therapeutic doses will cause serious poisoning, accompanied by necrosis of the gastrointestinal tract, if diuresis does not occur.[22]

The necrotic processes in the kidney are entirely, and those in the alimentary canal are chiefly, confined to epithelial layers and are, in consequence, reparable like other purely desquamative lesions without cicatricial residue.

Death of patients or experimental animals with mercury poisoning is referable, in a large proportion of instances, to none of the pathologic lesions mentioned above, but to a condition resembling surgical shock.[1,9,15,21] In fact, this condition appears to be responsible for almost all, if not all, of the deaths which occur within the first few days after poisoning. This is true of experimental animals as well as accidentally poisoned humans.

Treatment has, in general, been directed almost entirely to promoting elimination of the poison from or through the gastrointestinal tract by the administration of fluids perorally and by rectum, and by gastric lavage and colon irrigations,[1,9,16,26,28] procedures which are only secondarily intended to furnish fluids to the body and to allay the irritation and inflammation of the gastrointestinal tract by removing its cause, mercury. Instead of combating shock or providing with certainty for the restoration of the materials lost from the body by reason of vomiting and diarrhea, these cleansing measures are well constituted to exaggerate these losses. Some slight exception to this statement may be taken in behalf of those[9,10,12,26,29] who have advocated and employed the intravenous injection of saline solutions.

Sansum,[27] in 1918, with the idea that the provision of a large volume of fluid immediately after poisoning by mercury might mitigate the effects of the poison by accelerating its excretion, gave intravenous injections of various solutions to dogs shortly after they had received intravenously 4 mg. of bichlorid per kilo, enough to cause death without producing anuria. The injections caused profuse diuresis without any effect on mortality. Haskell,[10] in 1923, found that if dogs were given large amounts of saline intravenously after the administration by stomach tube of lethal doses of bichlorid, 20 mg. per kilo, a large proportion survived. There are certain distinctions between these apparently contradictory experiments that may be significant. Presumably the intravenous bichlorid given by Sansum was conveyed to the kidney in high concentration immediately and had caused irreparable damage before the intravenous fluid could act. The peroral mercury given by Haskell was probably absorbed gradually, so that no large amount was present in the blood at any given time. Under these circumstances the intravenous injections, by promoting diuresis, were able to sweep out mercury through the kidneys in sufficient dilution to prevent or mitigate the usual tubular necrosis. Haskell furthermore not only attempted to prevent early vomiting, but also continued his injections, intravenously or intraperitoneally, at intervals of 24 hours or less, thus insuring an adequate supply of fluids to replace those lost by vomiting and diarrhea.

In patients who, having survived a period of several days of anuria, die subsequently[1,5,16] the urine volume usually remains scanty, azotemia persists and edema is not infrequent. The few blood chemical examinations which can be found in the literature show that in this state the constitution of the blood is profoundly altered.[5] Postmortem examination may reveal extensive reparative processes, especially in the kidneys, where the tubular epithelium may be largely regenerated.

Although the necessity of furthering elimination of the poison is not to be neglected, it has become increasingly evident in the course of this study that major emphasis must be placed on the restoration and maintenance of an optimum internal environment and the prevention or rectification of the functional disturbances caused by mercury. Consideration and study of these factors has led to repeated modification of therapeutic measures, with the final adoption of a rather radical procedure which, in its entirety, has been employed in the treatment of only 3 cases. The chief aims of the treatment, after the usual preliminary measures have been employed to remove poison from the stomach, are: to prevent shock, to prevent fluid depletion by reduction of vomiting and diarrhea, to replace fluids lost on account of these symptoms, to furnish sufficient fluids to favor the production of a large urine volume, to prevent starvation acidosis and to mitigate protein destruction and to pro-

duce and maintain an internal environment as nearly normal as possible. It is believed that such an environment must exert a favorable influence, if for no other reason, because it will better enable the subject, if he survives the first acute impacts of the poison, to reap later the full advantages of the reparative processes.

The first point which demands consideration is shock, which may come on early and has usually been ascribed to trauma of the gastrointestinal tract. Although this may play its part in precipitating shock, fluid loss by vomiting and early diarrhea may be quite as important. Among the survivors in Table 1 it will be seen that Case 61806, within a short time after taking mercury, and without any treatment other than emesis and lavage, had serum proteins of 8.46 per cent and chlorids of only 92 milliequivalents, indications of hemoconcentration and chlorid depletion. In Case 51558, although the serum proteins are not initially abnormally high, 7.12 per cent, they are distinctly higher than they are 36 hours later, when the patient has received fluids and is voiding freely. Among the fatal cases, 63408 and 41938 illustrate more extreme pictures of the same kind. In the former a blood cell volume of 60.2 per cent renders it the more likely that the high protein value is due to inspissation of the blood. In these cases distinct alkali deficits are evidenced in bicarbonates of 19.2 and 21.7 milliequivalents, respectively. Chlorid is normal in Case 63408, somewhat reduced in Case 41928. The differences in the relative degree of depletion of Cl and HCO_3 depend on the proportions of fluid lost by stomach and by bowel. Vomiting, if the gastric acid secretion is active, will tend to carry out more Cl than base; diarrhea will cause more rapid wastage of sodium. Case 63408, with normal serum chlorids and the lowest bicarbonate, had profuse diarrhea by the time of the blood examination; the others, with chlorid deficits, but less acidosis, had vomited, but had not developed diarrhea.

Whether the blood inspissation be due to loss of fluid in gastrointestinal secretions or to transudation from the vessels such as occurs in shock, it is clear that a situation is early produced which must have an extremely unfavorable influence on the formation of urine. In fact, it is not improbable that initial anuria or oliguria may be due quite as much to reduction of body fluids and low blood pressure as to the destructive effect of mercury on the kidneys. Whatever measures may be employed for the removal of the poison from the alimentary tract, it would seem most rational at this stage to give a large volume of saline parenterally, a procedure which has, indeed, been frequently advocated.[9,26,29] Early attempts at treatment in this series were directed chiefly toward the support of the fluid and salt stores of the subject and the provision of a large volume of fluid for the production of urine. All patients who continued to vomit after the initial lavage and were unable to take

fluids freely, as well as those who developed diarrhea early, were given large volumes of saline and glucose solutions subcutaneously or intravenously at the earliest possible moment. Ultimately the parenteral administration of fluids as soon as lavage had been completed was made a routine procedure. Those who did not vomit or exhibit diarrhea and who were able to take fluids freely by mouth from the first were given extremely large volumes of water, salty broth and carbohydrate drinks perorally. The quantities of fluid given and the urine volumes produced are indicated in Table 2.

Some idea of the amounts of fluid lost by vomiting can be gained from the magnitude of the apparent positive fluid balances during the first and second days, and also from measurements of vomitus. The immediate generous response of the kidneys is exhibited in the large urine volume. It does not seem unreasonable to suppose that this method of treatment served to minimize the occurrence of shock, to place the organism in a favorable position to resist the general systemic effects of poisoning and, by the establishment of diuresis, to facilitate the rapid excretion of the mercury. Possibly this has something to do with the fact that the survivors in this series were so peculiarly free from symptoms and so sharply differentiated in this respect from the fatal cases. Cases 72767, 72763 and the second observation on Case 51558 (Table 1) show that the chemical composition of the serum after such treatment is relatively normal. The importance of this evidence must, however, be discounted because of the uncertainty concerning the severity of the poisoning in all patients who recovered without symptoms.

The electrolyte patterns in the fatal cases are sharply distinguished from those of survivors. They are characterized by progressively falling serum proteins, low bicarbonate, chlorid and base, with phosphate usually elevated. Reduction of bicarbonate, chlorid and base can be referred, like the similar changes in patients who recovered, to loss of salts in vomitus and feces. The hypoproteinemia is not so easily explained. Loss of protein through the kidneys can be at once excluded because all the patients had anuria or extreme oliguria. Protein starvation may be responsible for reductions late in the course, for example, in the last days of Cases 61163 or 73165; but hardly explain the low value found in Case A–2855, only 12 hours after poisoning. That loss of protein into the intestinal contents cannot be the sole cause of the serum protein deficits is clearly demonstrated by the data on Cases 61385, 44720 and A–6100. In the last 2 patients, especially, serum proteins fell in the absence of diarrhea.

Erlanger[6] first pointed out that in the later and more severe stages of shock the vessel walls become permeable to proteins, which, therefore, escape from the blood serum into the transudates. In this stage the serum proteins and blood volume diminish simultaneously. Blalock[3] finds that transudation of proteins may occur in

a variety of conditions analogous to shock, especially when the blood pressure is low or falling and that, in these circumstances, intravenous injections of salt or sugar solutions may tend to accelerate the escape of serum proteins. The rapidity with which hypoproteinemia developed in these cases, and especially in Cases A–2885 and 73165, is highly indicative of such a seepage of proteins from the vessels. It is obvious that once such a process is instituted a peculiarly vicious cycle has been established, because the force opposed to transudation, the effective colloid osmotic pressure, the difference between the concentration of protein in the blood serum and that in the interstitial fluids, is doubly reduced by reason of the fact that the interstitial fluids receive the protein lost by the serum.

The importance of shock as a feature of early severe mercury poisoning can be illustrated best by certain examples:

Case Reports. Case 1.—(A–2885.) A woman, aged 55 years, took 5 bichlorid tablets with suicidal intent. About 1½ hours later she was found in the cellar, vomiting and having watery bowel movements. She was brought immediately to the hospital in a condition of shock, with cold hands and feet, cyanosis, distant heart sounds, an almost imperceptible, rapid pulse and a systolic blood pressure which could not be determined with certainty, but seemed to be about 80 mm. She was still vomiting pink, mucoid material and passing reddish, watery stools. Seven hours later, in spite of the subcutaneous administration of 2500 cc. of saline, she had passed no urine, was still in extreme shock with undetermined blood pressure and the subcutaneous fluid had not been completely absorbed. Continuous intravenous saline infusion was instituted. This brought the blood pressure up to 70/58; but as soon as the infusion was interrupted the pressure fell precipitately. For this reason 17 hours after admission she was given a transfusion of 250 cc. of blood. The blood pressure rose to 88/58, shortly after which she voided about 25 cc. of urine. The improvement in the circulatory condition was maintained for about 48 hours. Vomiting ceased and she was able to take fluids by mouth, but diarrhea and anuria persisted. Two and a half days after admission she again went into shock with falling blood pressure and died. The serum electrolyte study in Table 1 was made shortly before the continuous intravenous infusion was begun.

By the time this patient had come to the hospital she already had shock of sufficient severity to preclude the passage of urine. The administration of saline in this condition was of little value as is evidenced by the fact that it was not even absorbed. That the intravenous infusion was doomed to failure when the serum proteins and blood pressure were both so low is obvious. Blood transfusion given far earlier might have reëstablished circulatory efficacy and blood volume at a time when restoration of these functions would have been of more benefit. The early stories of Cases 41938 and 61163 are similar. Case 63408, in spite of an early transfusion of 250 cc., could not be brought out of an extreme state of shock, which proved fatal after about 18 hours.

From these examples and what is known of the physiology of shock one can conclude that, although intravenous administration

TABLE 1.—SERUM ELECTROLYTES IN A GROUP OF CASES OF MERCURY POISONING.

Hosp. No.	Time since poisoning.	Blood.			Serum.							
		Nonprotein nitrogen, mg. per cent.	Oxygen capacity, vol per cent.	Cell volume, per cent.	Protein, per cent.	Albumin, per cent.	Globulin, per cent.	HCO_3, m.eq.	Cl, m.eq.	Inorganic P, m.eq.	Total base, m.eq.	
						Survivors.						
72767	57 hrs.	22	16.9	38.5	6.68	5.09	1.59	28.8	101.2	..	152.5	Large amounts of fluid by mouth and subcutaneously.
72673	12 hrs.	22	...	42.6	7.05	4.87	2.18	23.1	104.2	...	...	Large amounts of fluid by mouth and subcutaneously.
62494	Few min.	20	...	...	...	...	...	20.3	109.2	3.9	157.0	After vomiting and lavage.
61806	Few min.	33	...	...	8.46	6.02	2.44	25.3	91.8	1.7	156.8	After vomiting and lavage.
51558	90 min.	...	...	...	7.12	...	...	24.4	98.0	2.6	150.0	After vomiting and lavage.
	36 hrs.	28	...	...	6.21	3.98	2.23	29.5	97.2	1.9	148.0	After large amounts of fluid orally and subcutaneously.
						Fatal cases.						
29576	9 days	303	12.3	26.0	6.56	...	...	10.4	57.0	16.9	...	No treatment.
A-2885	9 hrs.	67	...	...	4.38	1.09	3.29	12.4	114.2	2.5	143.6	Vomiting and diarrhea; subcutaneous glucose and saline.
63408	4 hrs.	46	...	60.2	7.72	4.88	2.84	19.2	101.8	2.4	155.1	Vomiting and lavage; diarrhea and anuria; in shock.
41938	3 hrs.	43	20.6	42.4	9.44	...	...	21.7	96.3	...	150.0	Vomiting and lavage; in shock.
	4.5 days	165	12.9	32.3	4.98	...	...	11.7	101.3	...	143.0	Diarrhea and anuria; received little fluids.
61163	36 hrs.	66	...	...	6.33	4.54	1.79	...	90.0	...	...	Vomiting, diarrhea, anuria; some parenteral fluids.
	7.5 days	158	...	...	4.44	3.43	1.06	...	82.4	...	...	Vomiting, diarrhea, oliguria; parenteral fluids.
73165	14 hrs.	63	...	41.8	5.20	3.57	1.63	18.2	90.7	1.9	124.0	Vomiting, diarrhea, oliguria; parenteral fluids.
	4.5 days	90	...	...	5.30	3.82	1.48	9.3	88.8	3.9	121.0	Vomiting, diarrhea, anuria and edema; parenteral fluids.
	7.5 days	144	...	28.4	4.50	3.11	1.39	10.1	93.0	5.2	130.0	Vomiting, diarrhea, oliguria and edema; parenteral fluids.
	9.5 days	175	...	...	4.72	...	...	23.7	98.8	...	...	Vomiting, diarrhea, oliguria and edema; parenteral fluids.
	11.5 days	212	...	26.5	5.04	3.50	1.54	10.3	98.0	7.3	142.0	Vomiting, diarrhea, oliguria and edema; parenteral fluids.

The 3 last cases of the series of survivors are given in Table 3.

of saline may be of value in the early treatment of mercury poisoning without shock, it must be employed as a temporary expedient and with care if the blood pressure shows a tendency to fall. If signs of shock appear immediate blood transfusion would seem to be the logical procedure. Subcutaneous injections of fluid are safer than intravenous; but, because the fluid is more slowly absorbed, may not have so rapid a diuretic effect. In some instances the authors have felt that they were able to avoid some of the ill effects

TABLE 2.—FLUID INTAKE AND OUTPUT OF RECOVERED CASES IN EARLY STAGES.

(Records for the first day seldom include more than a fraction of the 24 hours, because this period covers from admission to 7 A.M. of the next day.)

Hosp. No.	Parenteral fluids on 1st day.[a]	Vomiting persisting more than a few hours	Fluid intake, cc.			Fluid output, cc.		
			1st day.	2d day.	3d day.	1st day.	2d day.	3d day.
68155	0	0	6,000	8,700	7,500	3310	8,100	5900
84957	S 2000	0	4,400	10,300	5,200	700	3,400	3300
82858	S 3000	0	6,950	7,480	7,950	3550	5,850	4600
22593	S 2500 I 3500	0	8,800	12,530	6,690	2050	9,010	7650
53740	0	0	700[1]	6,500[1]	4,600	3200	2,340	2100
72767	S 3000	...	3,400	12,450	6,000	500	5,330	5380
72673	I 400	0	16,900	...	...	8810		
81314	S 3000	Once or twice	5,250	5,400	5,100	3550	3,000	3900
36688	0	+[2]	1,800	3,300[3]	2,600	...	1,920	1140
56592	0	0	1,400	4,460	3,100	1000	425	1000
4511	S 5000	0	8,500	8,900	5,100	7800	8,900	5800
10295	0	0	5,000	5,000	4,800	3200	3,000	2600
62494	S 1500	+[4]	12,800	12,900	12,100	7500	9,100	8800
61806	S 3000	0	5,400	10,280	6,100	1590[5]	4,060	3310
51558	0	+	...	7,860	8,800	...	2,980[6]	5470
70851	S 3000	+	6,000	13,800	14,800	2500	11,110[7]	8900

[1] Intake and output on 1st day includes 12 hours; on 2d day 3000 cc. fluid subcutaneously.
[2] Vomiting on first 2 days due to renal colic.
[3] Fluid subcutaneously on 2d day.
[4] On 1st day vomited at least 1000 cc.
[5] Vomited 1400 cc.
[6] Fluid subcutaneously on 2d day; vomited 1050 cc.
[7] On 2d day vomited 1500 cc.; received 3000 cc. subcutaneously.
S, subcutaneously; I, intravenously.

and reap some of the benefits of large infusions, by giving small or moderate amounts of hypertonic (10 to 50 per cent) glucose solution intravenously and simultaneously injecting saline subcutaneously. The well-recognized anemia which regularly develops in all cases of severe mercury poisoning affords another indication for transfusion.

Those patients who survive the first impacts of poisoning can, apparently, be divided into 2 groups: those that have continuous

anuria, in whom death is usually attributed to uremia; others who never develop complete anuria, or, after a period of anuria of variable length, resume urination, passing small volumes of urine, but never attaining adequate excretory function. There are in the literature a few extensive studies of blood chemistry in such cases. The outstanding disturbances are persistent or increasing azotemia and reduction of serum chlorids and bicarbonate.[2,5,12,17] Hayman and Priestley,[12] and Sunderman, Austin and Camack[28] found in 1 case that serum base and proteins were also low. Similar disturbances are found in the last 2 fatal cases in Table 1.

It seems most plausible to ascribe the salt depletion to the effects of diarrhea and vomiting, the hypoproteinemia to the factors which have been discussed above and, in addition, to malnutrition which results from these same symptoms. How serious the salt losses may become is illustrated by Case 73165 (Table 1).

CASE 2.—The patient, a woman, aged 47 years, on March 20, 1929, at 6.30 P.M., swallowed 5 7.5-grain tablets of bichlorid of mercury. She did not vomit until 6.50, when an attempt was made to insert a stomach tube. She was brought at once to hospital, where she was given water, eggs and milk, followed by a gastric lavage. At this time her blood pressure was 160/110. By 7.30 the pressure had fallen to 138/90 and she presented symptoms and signs of shock: extreme weakness and cold clammy skin. She was still vomiting material which contained blood. She was given 3000 cc. of saline subcutaneously and 500 cc. of saline and 500 cc. of 5 per cent glucose intravenously. During the night she took fluids poorly, vomited frequently, had watery diarrhea and passed only small amounts of urine at infrequent intervals. In spite of the enormous quantity of salt which she had received, by the next morning (Table 1), 14 hours after taking the poison, the serum proteins, chlorids, bicarbonate and base were found greatly reduced. The cell volume, 41.8 per cent, and a red blood cell count of 5,000,000 clearly proved that these disturbances were not due to hemodilution. After this she was given intravenous saline infusions of about 1000 cc. daily through the 29th (on the 22d 3000 cc. were given by infusion); besides this, subcutaneously, on the 21st 6000 cc., on the 22d 3000 cc. and on the 23d 5300 cc. and on the 26th 3000 cc. of saline and 5 per cent glucose solution. Altogether she received about 30 gm. of sodium chlorid parenterally daily for the first 5 days. Nevertheless, the salt in the blood continued to diminish. Meanwhile she vomited continuously, sometimes as often as 20 times a day, and, in spite of 2 colon irrigations a day, had from 6 to 22 stools. The urine volume, which had been 1160 cc. on the 21st, dwindled steadily. Exact measurement was, for a time, impossible, because so much was voided with stools. However, complete collections were made on 6 separate days after the 24th and the urine volume was found to vary between 40 and 375 cc., with an average of 165 cc. After about 4 days she developed edema. For this reason subcutaneous injections of fluid were, for the most part, discontinued; parenteral fluid administration was limited to a daily infusion of about 1 liter of saline (an exception was made on the 26th when she received 3000 cc. of saline and glucose by hypodermoclysis). The diarrhea and vomiting nevertheless continued and the urine volume remained small. The edema diminished, but did not entirely disappear. The serum proteins had fallen further and the serum salt deficit persisted. On April 31, 10 days from the onset, she was given a transfusion of 450 cc. of blood.

At this time she was in a desperate condition and quite waterlogged. Attempts to administer fluids and food by mouth were discontinued. Although the vomiting diminished promptly, the diarrhea persisted, the urine volume remained small and she died on April 2, 13 days after admission.

In this case and in Case 61163 (Table 1), which was quite similar, it is evident from the frequency and volume of vomitus that the nutritive value of the food and fluids taken must have been negligible. Indeed it was not inconceivable that, acting as stimulants in the stomach, these materials only caused the secretion of extra salt and fluid which was vomited. In the stomach, and probably in the small intestine, there is a tendency for fluids to be brought into osmolar equilibrium with the blood before or during the process of absorption. Unless, therefore, the fluids and food given were isotonic with the blood, salt, at least, would pass into them and, if they were not retained, would be lost in the vomitus. If giving food and fluids has no nutritive value because of emesis, it becomes tantamount to lavage. As a means of removing poison this might be advantageous were it certain that excreted mercury, after the initial stage, attains a sufficient concentration to produce any serious damage or that it is further concentrated in the process of reabsorption. Whether it does or not, there is grave doubt whether this hypothetical damage is to be weighed heavily against the disorganization of the body fluid composition which results from efforts to dilute or remove the poison by emetic measures or lavage. The theory that fluid administration or lavage allays gastric irritation has even less physiologic support. It has been repeatedly demonstrated that animals with pyloric obstruction can be kept alive for long periods if the fluid lost in the initial vomitus is replaced by saline and no fluids are given by mouth. After the initial irritative vomiting under these conditions gastrointestinal secretion practically ceases. Whether the same would be true of a stomach with a necrotic mucous membrane could not be predicted, but it seemed justifiable to make the test in view of the unfortunate outcome of most patients who had been subjected to the conventional forms of treatment. What has been said of gastric lavage and the promotion of emesis may be equally true of colonic irrigations and encouragement of diarrhea.

In a case reported by Hayman and Priestley,[12] under the Lambert and Patterson treatment, at the end of 6 days of anuria urine flow was resumed, but was inadequate. The blood nonprotein nitrogen continued to mount, finally reaching 247 mg. per 100 cc., while chlorid, bicarbonate, base and protein of the serum were greatly reduced. Meanwhile there had been diarrhea. At this point the Lambert and Patterson treatment was discontinued and daily saline infusions were given instead. Immediately the urine volume and nitrogen excretion increased, the blood nonprotein nitrogen fell and the patient made a rapid and uneventful recovery. The improvement

which Hayman and Priestley attribute to the saline infusions may have been quite as much due to interruption of the colonic irrigations. Choisy and Perrot[5] have reported a case that died at the end of 49 days. After an initial 3-day period of anuria urination was resumed, but the volume remained small, the blood nonprotein nitrogen continued to rise and, after a period of apparent clinical improvement, she developed mental symptoms, extreme asthenia, anorexia, finally edema. From the onset the serum chlorids were low and remained so until death, except for transient responses to subcutaneous and intravenous saline. Little salt was given parenterally, although she received small daily infusions of hypertonic glucose. From what is known of the rapidity of regenerative processes in mercury poisoning it seems difficult to attribute death in this case directly to the effects of this metal. Landau, Glass and Beiles,[17] who have recognized the salt deficiency which results from the gastrointestinal effects of mercury, claim that the administration of bismuth in large doses (as much as 9 gm. daily) greatly reduces mortality.

In spite of all theoretical considerations, withholding all fluids and omission of lavage and colon irrigations marked a radical break with authority and convention that took no small courage. Happily an opportunity to test the theory in an analogous situation without so serious a breach of convention presented itself at this point:

Case 3.—A patient* was admitted to the hospital in shock with extreme intravascular hemolysis, oliguria and hemoglobinuria. She had attempted to induce abortion by intrauterine injection of lysol after some pills given by a friend had not proved immediately efficacious. Like the mercury cases cited above she passed, for some days, only small amounts of urine containing little nitrogen, and the nonprotein nitrogen of the blood rose steadily. Throughout this time she suffered continuously from epigastric distress and vomited all food and fluids. The vomitus was bloody. In spite of infusions and hypodermoclyses of glucose and saline the serum chlorids fell to 93 milliequivalents. Furthermore she became distinctly edematous. Finally, after 7 days, the administration of food and fluids by mouth was entirely stopped, and she was given daily infusions consisting of 1000 cc. of 10 per cent glucose and an equal amount of saline. Vomiting ceased almost immediately, the urine volume increased rapidly, her condition improved and the blood nonprotein nitrogen diminished. For 4 days, as long as the epigastric pain persisted, the treatment was continued. At the end of that period she was able to eat and drink without vomiting and the infusions were discontinued.

These experiences led to the adoption of an entirely new course of procedure in the treatment of mercury poisoning, which has now been employed on 3 cases. The general principles involved are: (1) Initial administration of protein and gastric lavage, as before; (2) a large intravenous infusion of saline at the earliest possible moment; (3) blood transfusion if evidences of shock appear; (4) if this cannot be effected at once, simultaneous intravenous injection

* This case will be reported more fully in connection with a study of blackwater fever. The intravascular hemolysis may have been caused by quinin.

of 10 per cent glucose and subcutaneous injection of saline may be used as a temporary expedient; (5) subsequent saline and glucose injections and transfusions in quantities and at intervals so regulated as to insure the presence in the body of a large, but not excessive, supply of fluid of nearly normal composition and to maintain circulatory efficiency; (6) from the onset no fluids are given by mouth as long as there is nausea or vomiting. If there is no diarrhea, rectal treatments are omitted. A single small cleansing enema may be given daily if there is diarrhea, if such treatment seems to relieve the diarrhea, as it sometimes does.

CASE 4.—(44720.) A man, aged 32 years, while intoxicated, took some bichlorid of mercury tablets (he claimed that he had taken 3, but it is doubtful whether he actually took more than 2 and he may have taken only 1), at about 8.50 P.M., March 24, 1932. He arrived in the Accident Ward of the New Haven Hospital at 9.19 P.M., having vomited twice on the way. His blood pressure on admission was 135/100 and general physical examination revealed no important abnormalities. After the usual treatment with protein and gastric lavage he was given, by intravenous infusion, 1500 cc. of saline. At 10.20 P.M. his blood pressure was 120/80. At 10.50 P.M. he was given another infusion of 1500 cc. of saline and simultaneously 1500 cc. of saline and 1500 cc. of 5 per cent glucose subcutaneously. Shortly after the infusion his blood pressure was found to have dropped to 96/64. He was therefore given, at 1 A.M., on March 25, a transfusion of 275 cc. of blood which brought his blood pressure up to 110/90. After the transfusion he had a chill, vomited and at 2.45 A.M. passed dark, bloody urine in which no red blood cells were found.* Between admission and 11 P.M. he had 3 involuntary watery stools and vomited at intervals. For this reason he was allowed to have nothing but cracked ice by mouth. At 4 A.M. the vomitus contained changed blood. Until 5.30 A.M. he passed large amounts of urine without difficulty, but after this did not void again until 1 P.M., after he had been given intravenously 1000 cc. of 10 per cent glucose solution. A similar injection was given at 3 P.M., when there was again evidence that diuresis had been interrupted. After this the urinary volume did not again diminish. After the first 3 bowel movements diarrhea ceased. There was occasional vomiting throughout the 25th, but none after the early morning of the 26th. It was, therefore, possible, after 9 A.M. on the 26th, to discontinue parenteral administration of fluids and to give both food and fluids by mouth. He complained throughout the 25th and 26th of soreness of the mouth, burning in his throat and pains in the loins. These complaints continued through the 27th and by the 28th he had a well-marked stomatitis. Diarrhea recommenced on the 29th and in the course of the day he had 7 loose stools.

On the 30th he vomited large amounts of fresh blood twice and the stools became tarry. Finally at 11 P.M. he had a third gastric hemorrhage succeeded by symptoms of shock. At 1.30 A.M., March 31, his blood pressure was only 90/60. He was, therefore, given, at 2.30 A.M., an infusion of 500 cc. of 10 per cent glucose, followed by a transfusion of 300 cc. of blood. This relieved shock symptoms and restored the blood pressure. All fluids by mouth were, of course, discontinued for 24 hours and large volumes of glucose and saline were given subcutaneously. For the next 2 days hypodermoclyses were continued, but the patient was allowed water by mouth. For 2 days the tarry diarrhea persisted.

After April 1 all symptoms ceased, the stomatitis rapidly cleared and

* In spite of the obvious hemolytic reaction, repetition of agglutination tests seemed to indicate no incompatibility between the blood of donor and recipient.

recovery was uneventful. On April 2 a small transfusion was given to accelerate recovery and Sippy diet was instituted.

The urine immediately after the first transfusion was quite typical of extreme hemoglobinuria and the next few specimens contained changed blood pigment and detritus. Very faint traces of albumin, leukocytes and occasional casts persisted in the urine through April 9.

When discharged, April 12, the only symptoms were fatiguability, probably referable to anemia, and nocturia. April 25, when he was seen in the dispensary, he seemed entirely well except for a moderate anemia.

The record of treatment with some notes on excretory function are presented in Table 3, the results of blood chemical examinations in Table 4.

TABLE 3.—RESULTS OF CHEMICAL EXAMINATION OF THE BLOOD.

Date.	Time.	Blood.			Serum.						
		Oxygen capacity, per cent.	Cell volume, per cent.	Nonprotein nitrogen, mg. per 100 cc.	Protein, per cent.	Albumin, per cent.	Globulin, per cent.	Bicarbonate, m.eq.	Chloride, m.eq.	Inorganic phosphorus, mg. per 100 cc.	Total base, m.eq.
				Case 44720.							
Mar. 24	10.50 P.M.	..	..	42	8.16	5.27	2.89	23.6	99.4	3.5	144.1
25	8.00 A.M.	..	..	43	8.53	5.78	2.75	25.2	96.5	3.4	147.7
	12.15 P.M.	22.2	52.6	49	8.22	5.95	2.27	23.0	98.3	2.8	143.9
	5.00	20.3	47.9	42	7.18	4.96	2.22	23.2	97.0	3.5	140.5
26	9.00 A.M.	18.7	41.8	59	6.42	4.32	2.10	24.2	98.8	3.4	140.7
27	9.00	..	..	69							
28	9.00	16.0	37.9	75	5.61	3.90	1.71	25.2	99.1	4.9	144.7
29	9.00	16.2	37.7	95	5.62	4.01	1.61	25.9	98.6	5.6	142.7
30	9.00	13.1	28.4	85	4.96	3.61	1.35	23.1	101.4	6.2	147.8
31	2.00 P.M.	..	..	81							
April 1	2.00	8.1	19.6	63	5.17	3.30	1.87	22.9	104.2	4.0	145.1
2	2.00	6.7	15.8	46	4.53	3.08	1.45	23.3	105.5	3.5	147.5
25	9.00 A.M.	13.8	34.6	28	7.09	4.57	2.52	27.1	102.6	3.4	
				Case A-6100.							
Mar. 29	9.15 P.M.	..	54.3	69	7.44	5.45	1.96	16.8	97.8	4.8	141.1
30	7.15 A.M.	21.3	49.0	63	6.04	4.61	1.43	17.3	104.0	5.5	139.2
31	7.15	17.3	39.5	85	5.22	3.66	1.54	17.3	98.2	4.1	137.3
April 1	9.00	17.0	39.8	97	5.39	3.66	1.80	15.0	91.6	4.5	132.9
3	2.00 P.M.	..	..	140	5.47	3.80	1.70	13.7	95.8	6.9	138.8
5	9.00 A.M.	16.7	38.3	130	5.66	3.95	1.70	15.1	95.5	7.4	139.3
6	9.00	..	..	141	5.95	3.84	2.12	16.4	93.9	6.7	136.5
8	9.00	16.3	35.1	128	6.63	3.69	2.97	17.1	102.0	8.5	142.0
11	9.00	17.4	41.3	117	7.37	4.02	3.34	16.1	100.0	7.9	145.0
14	9.00	..	31.8	120	5.98	3.26	2.70	14.9	97.5	7.1	136.5
19	9.00	12.7	29.0	84	5.64	3.29	2.35	17.7	102.0	6.1	137.3
25	9.00	..	..	35	4.77	3.24	1.53	23.5	99.9	3.2	141.3
				Case 61385.							
May 10	9.00 A.M.	..	..	30	6.96	5.09	1.84	25.9	100.9	3.0	
11	9.00	19.0	48.3	30	6.76	4.88	1.88	25.0	99.0	4.3	
12	9.00	16.1	40.5	23	5.45	4.05	1.40	26.2	103.1	3.0	

TABLE 4.—CLINICAL DATA OF CASE 4 (44720).

"Time," in relation to parenteral fluids, until after 8 A.M., March 26, indicates approximately the time at which injections were begun: "time," in relation to excreta, represents the time at which these were collected.

Date, 1932.	Time.	Fluid intake.			Fluid output.			Chlorid.				Blood pressure.
		Intravenous, cc.	Subcutaneous, cc.	Oral, cc.	Urine, cc.	Vomitus, cc.	Feces, cc.	Intake, gm.	Urine, gm.	Vomitus, gm.	Feces, gm.	
Mar. 24	9.00 P.M.	1500	...	...	...			13.5	...			135/100
	10.00	1500	...	...	650		3 lost[4]	13.5	5.0		3 lost[4]	120/80
	11.00	...	3000	...	640			13.5	6.0			128/118
	12.00	...	...	...	880			...	7.8			92/64
Mar. 25	1.00 A.M.	350[1]	...	200[2]	400	1700	...	0.7	3.9	2.6	...	110/90
	3.00	...	...		370		...	...	4.5		...	110/85
	6.00	...	2000		130		...	13.5	1.7		...	107/82
	11.00	1000	...	250[2]	...		...	...	...		...	115/90
	1.00 P.M.	...	...		290		...	...	2.2		...	130/100
	3.00	1000	...	250[2]	...		...	...	...		...	130/95
	4.00	...	...		270		...	...	1.8		...	125/90
	5.00	...	2000		...		...	13.5	...		...	124/85
	6.00	...	...		155		...	...	1.0		...	124/85
	8.00	...	...		100	560	...	...	0.7	1.2	...	125/80
	9.00	...	...	500[2]	105		...	...	0.8		...	130/85
	11.00	...	...		100		...	...	0.6		...	125/95
Mar. 26	3.00 A.M.	...	...		155		...	...	0.8		...	130/95
	8.00	...	...		260		...	...	1.3		...	130/90
Mar. 26	9.00	...	...	4350	1035	...	100 gm.	0	1.8	0	...	130/85
to 27	9.00	...	...		...	...	...	...	...	...	...	130/90
to 28	9.00	...	...	4505	2494	...	0	2.4	4.7	0	...	135/95
to 29	9.00	...	...	4000	3130	...	0	2.5	4.9	0	...	130/100
to 30	9.00	600	...	3100	1800	100	1795	2.7	1.8	2.0	9.5	142/100
Mar. 31	2.00 P.M.	400[3]	5000	300	1380	1500		36.9	2.2	5.0		125/80
April 1	2.00	...	3000	2500	1260	721		27.0	3.3	1.2		120/65
April 2	2.00	...	3000	2550	1750	...	57	27.0	6.6	...	...	120/70

[1] Transfusion of 275 cc. blood with 75 cc. of saline.
[2] Cracked ice.
[3] Transfusion, 300 cc. blood with 100 cc. saline.
[4] Three involuntary watery stools lost.

It is obvious that as a test of therapeutic measures this case is not entirely satisfactory. In the first place the dose of mercury which he took is not certain and probably not large enough to prove lethal. He does, however, appear to have absorbed enough to produce definite signs of poisoning: diarrhea, vomiting, stomatitis, temporary reduction of urine excretion (on the morning of March 25) and accumulation of blood nonprotein nitrogen and serum inorganic phosphate. Early blood examinations reveal hemoconcentration (high serum proteins and cell volume). Early signs of shock appeared shortly after admission. Unfortunately the response to therapy and the symptoms and functional disturbances immediately succeeding the first transfusion are confused by the occurrence of hemoglobinuria. Later a still more serious complication is introduced by the gastric hemorrhage. It may be argued and it was greatly feared that this might be referable to the effect of withdrawal of fluids in the face of mercurial ulceration. However, by the time of this accident he had been for 3 days taking food and fluids freely without gastric symptoms. Moreover, it was found that the patient had attended the Medical Dispensary during the preceding summer for a condition that was suspected to be gastric ulcer. Roentgen confirmation was not secured because he ceased attending the clinic before Roentgen ray examinations could be made. Barium Roentgen rays taken just before his discharge from the hospital disclosed no signs of gastric ulcer; but, by this time he had been for some days on Sippy treatment, free from symptoms. Except for these adventitious conditions, the course was singularly free from the distressing signs and symptoms usually seen in poisoned patients.

Although the serum proteins, hemoglobin and cell volume fell and the nonprotein nitrogen rose even before the gastric hemorrhage, diarrhea and vomiting early ceased, urine volume was maintained, no edema developed and the electrolytes remained relatively normal. Alkali deficit never became important; serum chlorids were only slightly reduced in the early days, perhaps because the parenteral fluids contained too little sodium chlorid in proportion to glucose and water.

One might conclude that the patient had been enabled by the therapy to escape many of the miseries of poisoning, if not death itself, even in the face of hemoglobinuria and a gastric hemorrhage which was in itself a serious hazard. On the other hand it is almost possible to take the gloomy view that therapy was responsible for these accidents and that only divine grace saved him.

Case 5.—(A-6100.) A male, aged 60 years, at 6 P.M. on March 28, 1932, with suicidal intent, swallowed 3 mercury tablets dissolved in water. He vomited almost immediately and after this was unable to take any food and vomited all fluids. He also developed, within a very short time, a profuse diarrhea with frequent watery stools. This persisted until he was admitted to the New Haven Hospital at about 9 P.M., March 29.

Up to this time he received no treatment. On admission he appeared thin and extremely dehydrated; his blood pressure was 120/80, but rapidly fell to 106/82. He was given at once, by intravenous infusion, 1000 cc. of 10 per cent glucose solution, and by hypodermoclysis 3000 cc. of saline. The blood pressure at 10 P.M. was only 90/80, but rose again after 30 minutes, remaining for the rest of the night between 100 and 120 mm. From the onset he passed no urine. The diarrhea, which had persisted until his admission to the ward, ceased abruptly at this time and was succeeded by obstipation. Both anuria and obstipation persisted until April 2. On this day, after an enema, 469 gm. of feces were removed, and on the same day he passed 18 cc. of urine. After this the urine volume gradually increased.

From the outset he was able to take fluids by mouth, vomiting only once, on April 2. The first night he received only 900 cc. of carbohydrate fluids orally. The next day, March 30, he drank freely until late in the afternoon, when he was given a hypodermoclysis of 1500 cc. of saline, because he complained that he was too full to drink. March 31, because of the same symptoms, 4000 cc. of the total 5600 for the day were given parenterally. On April 1 he vomited a small quantity and was given 1200 cc. of saline subcutaneously. After the enema on April 2 he again had no bowel movements for 3 days. On the 6th and 8th he was given cleansing enemas because of the persistent obstipation. On the 9th he had a spontaneous bowel movement and after this developed a troublesome diarrhea. This consisted of the frequent passage of small watery spurts, at first containing fresh or changed blood, with considerable tenesmus. The volume of the stools was very small as is evident from the fact that the total weight of material passed in 18 movements on the 11th and 12th amounted to only 659 gm. The diarrhea, which was accompanied by low-grade fever, persisted when he left the hospital against advice on April 29.

The first urine voided on April 2 gave a heavy reduction for albumin and was loaded with cellular débris. Subsequent specimens contained diminishing amounts of albumin, cells and casts. The urine of April 28 had only a faint trace of albumin and an occasional hyalin cast.

In spite of the early anuria and obstipation and except for the later diarrhea, the patient was peculiarly free from symptoms. His only complaint for the first few days was a sense of fullness when he tried to drink large quantities of fluid and regret that he was given no nourishment but carbohydrate fluids. From April 6 on he ate a general mixed diet.

The chief data pertaining to therapy and to excretory function are presented in Table 5, the results of chemical examinations of blood in Table 3.

There can be little doubt that this patient received a toxic and possibly lethal dose of poison, 3 tablets in solution. That much of this was absorbed seems evident from the fact that he developed quite early all the symptoms of severe mercury poisoning: anuria, vomiting and diarrhea. The prognosis was peculiarly unfavorable because he received no treatment for more than 24 hours. The first chemical examination of the blood, immediately after admission, revealed a high degree of hemoconcentration (cell volume, 54.3 volumes per cent) with serious depletion of bicarbonate, chlorid and base and well-marked accumulations of nonprotein nitrogen and inorganic phosphate. Evidences of shock were slight and disappeared rapidly after administration of saline and glucose solutions without the need of a transfusion.

TABLE 5.—CLINICAL DATA OF CASE 5 (A–6100).

Date.	Fluid intake.	Fluid output.			Cl (as NaCl).				Blood pressure.	Sodium bicarbonate, gm.	Weight, kilos.
		Urine, cc.	Vomitus, cc.	Stools, number.	Intake, gm.	Urine, cc.	Vomitus, cc.	Feces, gm.			
Mar. 29	4900[1]	0	0	0	27.0	0	0	0	120/80	0	
30	4100[2]	0	0	0	13.5	0	0	0	120/90	0	
31	5600[3]	0	0	0	13.5	0	0	0	130/90	0.7	
April 1	2300[4]	0	232	0	11.6	0	0.7	0	130/80	2.0	66.9
2	1620	18	0	469 gm.[6]	4.0	0.1	0	0.1	140/100	2.7	67.5
3	2920	1032	0	0	16.2	5.4	0	0	150/100	0.6	67.9
4	3270[5]	2025	0	0	13.5	12.2	0	0	150/100	2.0	
5	3045	2398	0	0	3.1	13.9	0	0	...	0	
6	2090	3530	0	1[6]	9.3	20.0	0	0	...	0.6	
7	3145	3800	0	0	9.3	20.3	0	0	...	0	62.0
8	3050	2560	0	1[6]	8.8	12.4	0	0	...	0	60.1
9	3930	1960	0	1	9.1	7.5	0	0	...	0	
10	1900	1500	0	2	6.6	4.5	0	0	...	0	60.3
11	4120	..	..	660 gm.[7]	9.7	0	0	0.9	170/100	2.0	58.7
12	1750	890	No further vomiting		9.2	1.2	0	0	148/98	2.0	58.7
13	2110	1260			8.0	2.6	No further vomiting	Feces not saved	...	2.0	58.8
14	2850	1740			8.0	2.6			...	2.0	58.6
15	2280	1720			6.0	6.6			136/90	2.0	58.5
16	3550	2260			8.4	6.9			130/90	2.0	57.6
17	3130	2090			8.9	6.4			128/88	2.0	57.3
18	2050	2110			8.5	6.3			...	2.0	57.3
19	2180	1800			8.1	6.0			...	2.0	57.4
20	1970	1580			8.3	5.9			...	2.0	57.3
21	1900	1700			7.1	5.6			...	2.0	57.0
22	2200	1680			6.6	4.7			...	2.0	57.1
23	1950	1480			7.7	4.4			...	2.0	56.5
24	1600	1210	..	..	8.8	4.6			...	2.0	56.2

[1] 1000 cc. saline intravenously; 2000 cc. saline and 1000 cc. 5 per cent glucose subcutaneously.
[2] 1500 cc. saline subcutaneously.
[3] 1500 cc. saline and 2500 cc. 5 per cent glucose subcutaneously.
[4] 1200 cc. saline subcutaneously.
[5] 500 cc. 10 per cent glucose and 1500 cc. saline intravenously.
[6] Result of enema.
[7] Onset of diarrhea: 13 stools on April 11, 5 on April 12.

It is not improbable that the administration of fluids during the first days was overemphasized. Although the patient developed no demonstrable edema during the anuria period, the rapid loss of weight in the first days following resumption of urination suggests that the body had been previously somewhat overloaded with fluid. That the balance between salt and water in the fluids given was also somewhat irregularly and imperfectly maintained is evidenced by the fluctuations in serum chlorid and base. Between the first 2 electrolyte studies the major portion of the fluid given was saline, which caused serum chlorid to rise to a rather high level. During the succeeding 48 hours larger amounts of water and less saline were given, causing serum chlorids and base to fall to a very low

level. Bicarbonate remained consistently low. The initial reduction of bicarbonate and base was presumably referable to diarrhea. The failure of these 2 components to rise after chlorid administration is natural. With ablation of renal function the ability to excrete the Cl ion of chlorid, retaining the base to reconstitute bicarbonate, was lost. Only by supplying bicarbonate as such could the electrolyte pattern have been restored to normal. Small quantities of sodium bicarbonate were given with this end in view, but this therapy was not pushed for fear of precipitating vomiting, which seemed a greater evil than the alkali deficit.

Withdrawal of oral fluids was not necessary in this case, for more than brief intervals, because vomiting had ceased by the time he entered the hospital. Restriction of oral fluids and substitution of subcutaneous and intravenous fluids were employed at intervals when nausea and vomiting threatened. There was, of course, no intention of producing such complete obstipation. How far treatment may have been responsible for the condition is uncertain. Restriction of the diet to easily absorbable sugars may have played a part. The results indicate that the patient recovered from most of his symptoms without the lavage processes usually employed and without the intervention of the bowel. This supports the theory that mercury causes its chief effects shortly after administration. It would certainly seem more advisable in future cases to employ enemata at daily intervals to assure removal of fecal accumulations and any poison that they might contain. Whether the diarrhea that developed on April 11 can be attributed to mercury is uncertain. June 1 the patient was in excellent health and stated that he had only intermittent brief periods of diarrhea. His wife volunteered that these seemed to occur only when he worked.

The wellbeing of the patient after treatment was instituted and his freedom from the usual distressing symptoms were most striking. One is forced to wonder whether vomiting and diarrhea and perhaps the constant lavage of the gastrointestinal tract are not responsible for some of the distress commonly experienced by subjects seriously poisoned with mercury.

The anuria and hypoproteinemia became progressively more severe, even after the blood nonprotein nitrogen had begun to fall. It is obvious that the initial fall of serum protein cannot be due to gastrointestinal protein loss. Hemodilution may have played a part. Between April 5 and 10 when the urine volume first became large the proteins rose sharply. The subsequent fall can, perhaps, be attributed to malnutrition resulting from inadequate diet and diarrhea together.

CASE 6.—(61385.) A married woman, aged 20 years, at 9 P.M., May 10, 1932, took 1 bichlorid tablet with suicidal attempt. She was almost immediately given egg white and mustard and vomited within 15 minutes. By 9.15 P.M. she was in the Accident Ward of the New Haven Hospital,

where she received gastric lavage, followed by an intravenous infusion of 1000 cc. of 10 per cent glucose solution and subcutaneous injection of 1500 cc. of saline and 500 cc. of 5 per cent glucose solution. Her blood pressure on admission was 137/76 and fell to 120/80 before she was sent to the medical ward. When she was still in the Accident Ward she voided 750 cc. of urine. Attempts to administer fluids by mouth provoked vomiting and were, therefore, discontinued at 2.30 A.M. At 5 A.M. she received by hypodermoclysis 2000 cc. of saline because of vomiting and mild diarrhea. During the night she urinated 4 times, twice with stools, and had 4 bowel movements. At 9 A.M. she appeared drowsy and complained of nausea and epigastric pain. Oral administration of fluids, which had been resumed at 8 A.M. was discontinued after a short time because of renewed vomiting, and she was given, in the course of the day, 1000 cc. of saline and 1000 cc. of 5 per cent glucose subcutaneously and 500 cc. of 10 per cent glucose solution intravenously. By evening nausea and diarrhea had ceased and she was able to take peroral fluids. Improvement continued through the night and by the morning of May 12 she was without symptoms and able to take a regular diet.

From admission until 10 A.M. the next morning the total excreta (urine, stools and vomitus) amounted to 1770 cc. and from 10 A.M. on May 11 to 7 A.M. on May 12, 3160 cc. It was impossible to separate urine and feces accurately. However, it is estimated that the second specimen contained about 600 cc. of fecal matter and 300 cc. of vomitus. The uncontaminated urine specimens which were collected contained no albumin and no significant microscopic abnormalities.

The results of chemical examinations are presented in Table 3.

In this case it seems reasonably certain that the dose of poison taken, though sufficiently large to cause diarrhea and vomiting, would probably have caused no serious damage nor proved a threat to life. The chemical studies show none of the common disturbances of the electrolyte pattern which have been demonstrated in some of the earlier cases of the series who had taken only enough poison to provoke vomiting. The administration of subcutaneous and intravenous fluids and the discontinuation of oral fluids in the presence of nausea and vomiting may have been instrumental in preventing such disturbances. It is interesting to note that, in spite of the absence of symptoms and functional disturbances, the serum proteins, hemoglobin and cell volume fall rapidly, reaching a distinctly subnormal level 36 hours after poisoning. By this time symptoms had disappeared and the urine output was quite adequate, making hemodilution rather unlikely. The consistency with which anemia and hypoproteinemia develop after mercury suggest some injury to the systems which control regeneration of red cells and serum proteins.

Summary. Although the outcome in these cases can in no sense be considered as a vindication of the course of therapy which has been proposed, the results in Case 5 (A–6100) at least justify the hope that it may prove superior to previous procedures. At least it seems reasonable to devote more attention to the functional disturbances that result from mercury poisoning, even if this necessitates a certain degree of moderation in eliminative measures. The

intention is not to propose a routine procedure, quantitatively measured and unalterably fixed for all patients alike; but rather general principles of treatment aimed against the most serious effects of the poison. The application of these principles and the emphasis placed on particular procedures must be adapted to the individual patient. It is obvious that this requires coördination of judgment and effort. The authors have frankly admitted that the ideal combination of these qualities was not attained in the treatment of the 2 serious cases described above. In Case A–6100 a point was stretched when the obstipation was allowed to continue, chiefly because as long as the general condition of the patient seemed so good it appeared justifiable to subject the treatment to an acid test.

It is believed that the general therapeutic principles which have been suggested are applicable to the treatment of other types of poisoning attended by gastrointestinal irritation or injury and renal damage, or in which the elimination of a poison which causes irritation or injury of the gastrointestinal tract may be facilitated by the production of diuresis. Its application in a case of phenol poisoning with hemoglobinuria has already been mentioned. More recently it has been employed successfully to combat the effects of rat poison (chiefly phosphorus) in another subject.

Conclusions. Major emphasis in the treatment of mercury poisoning has in the past been laid upon measures aimed to promote elimination of the poison through the gastrointestinal tract. Such measures have tended to exaggerate rather than to alleviate the functional and chemical derangements within the body which are caused by mercury. Chief among these are shock, reduction of the fluid content of the body and salt depletion.

General principles of treatment have been proposed, involving radical departures from previous procedures, which have as their chief aim prevention or alleviation of shock, dehydration and salt depletion, the provision of adequate body fluids of normal composition and the maintenance of optimal renal function.

The application of these measures in 3 cases is described in detail.

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OSTEOSCLEROTIC ANEMIA.

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The term osteosclerosis is understood to include those rare affections of the skeleton in which the bone marrow is encroached upon or obliterated by proliferation of connective tissue or deposition of bone, leaving the bones compact and dense but without change in their outward contour. Two types of the disease are recognized, that of so-called marble bones and myelosclerosis. The former, recently reviewed by Karshne and Pirie, seen usually in children and young adults, is hereditary and is characterized by a heavy deposition of bone of low phosphorus content advancing from the diaphyses. In the roentgenogram a homogeneous density, first compared to marble by Albers-Schönberg, obliterates the bony structure. A history of repeated fractures is frequently obtained.

The second type is not familial and multiple fractures have not been described. The pathologic process is largely a diffuse increase of connective tissue or trabeculæ in the marrow space, leaving the cortex still recognizable. The appearance of the bones in the roentgenogram is that of moderately increased density but with most of the cortex still evident. This contrast in the two types is shown in the accompanying illustrations.

Progressive osteosclerosis crowds out the marrow cells and often

produces a severe anemia with compensatory hemopoiesis in the spleen, liver or lymph nodes. Such a myelophthisic anemia may occur in either the Albers-Schönberg group or in myelosclerosis.

The purpose of this paper is to present 2 cases of this second type of osteosclerosis in which such an anemia was the outstanding feature. As descriptions of this type, except for Donhauser's report in 1908, have not been found in the American literature these cases are deemed to be of exceptional interest.

Case Reports. CASE 1.—An Italian, aged 42 years, entered the hospital on October 28, 1929, complaining of weakness for 10 months. He had been losing weight and strength and in May, 1929, gave up work to go to Italy, where his doctor placed him on a regimen of cooked liver. He improved somewhat but by the time of his return to Boston, in September, weight loss and dyspnea on exertion led him to enter the hospital. The tongue had not been sore and his diet had been well balanced.

In the *family history* no one had sustained fractures. One sister in Italy had had an anemia that responded to liver. He had 4 children who were healthy and their pelves, femora and knee joints showed no evidence of disease by roentgenogram.

In the *past* he had been well and strong and had broken no bones. The *occupational history* was interesting in that he had been a glass polisher for 12 years, using a buffing wheel with red oxid of iron as a rouge. A slight amount of dust was in the air about this wheel. No exposure to lead or benzol was suggested.

Physical Examination. He was well developed but undernourished and showed a sallow skin with a hectic flush over the malar eminences. The scleræ were clear and no petechiæ were seen. There was no glandular enlargement. The head, eyes, lungs and heart were normal. The blood pressure was 120 systolic and 80 diastolic.

The radials and brachials were not sclerotic and the fundi showed normal vessels. A moderately firm, nontender liver and spleen were felt at the costal margins. There was some tenderness on deep pressure over the medial condyles of the femora and extreme flexion of the knees and extension of the elbows were painful. The clavicles were prominent and seemed thickened. The remainder of the examination was not remarkable.

Laboratory Examinations. Urine: normal; no Bence-Jones protein. *Blood:* red blood cells, 2,500,000; hemoglobin, 45 per cent (Tallqvist); white blood cells, 4100 (polymorphonuclears, 54; lymphocytes, 38; mononuclears, 5; myelocytes, 3 per cent); blood smear (Wright) showed marked polychromasia with variation in the size and shape of the red blood cells (3 normoblasts were seen and the platelets were decreased); bleeding time, 6 minutes; clotting time, 2 minutes; fragility of red blood cells normal (B.H., 0.44 per cent; C.H., 0.32 per cent); average red cell diameter, 7.2 micra (dried smear). Hinton and Wassermann tests negative. Serum agglutinations negative in all dilutions for melitensis, porcine and bovine abortus. Blood cultures showed no growth on three trials.

Gastric analysis with ergamin normal. Liver function normal. (Rosenthal, 2 per cent retention in one-half hour.) Basal metabolic rate, +9. Roentgenograms of the heart and lungs were normal. A gastrointestinal series showed the duodenal cap slightly enlarged and the first portion of the duodenum small and flattened but no diagnosis was offered after second examination.

The pelvis, vertebræ, ribs and long bones showed diffuse increase in the bone density but the cortex could be distinguished. No fractures or areas of destruction were seen. The skull was normal.

Course. In spite of a persistent reticulocyte count of 1 to 3 per cent, the blood level did not change appreciably with liver and iron therapy. An afternoon fever of 99° to 100° F. continued while he was at rest in bed. Frequent sweats either in the day or night troubled him. A biopsy of a gland, 1 cm. in diameter, from the right supraclavicular area was diagnosed as chronic inflammation. In the period of 1 week three tarry, guaiac-positive stools were passed. This incident was never explained and with careful search no further blood loss was discovered.

After a 5 weeks' study a satisfactory diagnosis was not reached, but splenic anemia (Banti) was favored and exploration for splenectomy was advised but the patient decided to deliberate on this at home. The significance of the previous Roentgen examination had been overlooked at this time.

On May 6, 1930, he returned, saying that he has spent much of the time in bed, taking a high vitamin diet and 6 Blaud's pills daily. He complained only of weakness and pains in the joints. There had been no obvious blood losses. The heart was now found to be enlarged 10 cm. to the left in the fifth interspace and a low-pitched, systolic murmur was heard, loudest at the second left interspace. The spleen was 4 cm. below the left costal margin and a smooth liver edge was felt 4 cm. below the right mid-costal margin. Slight pitting edema was present over the ankles.

Repeated laboratory examinations showed no significant changes except for a red blood count of 1,300,000 and a hemoglobin of 25 per cent. The blood smears again contained numerous immature forms. Additional blood cultures and serum agglutinations for undulant fever were negative. A therapeutic trial with quinin did not alter the febrile course. Finally, aided by the previous roentgenologic report, the diagnosis of osteosclerotic anemia was made after bone marrow biopsies were done.

Biopsy Report (Dr. T. B. Mallory). *Bone Marrow.* Microscopic examination shows a very slight increase in the number and width of the bony trabeculæ. There is no osteoid tissue and no evidence of active bone formation. The spaces between the bony trabeculæ are filled with fatty and fibrous tissue with minimal numbers of myeloblastic cells. Scattered stem cells, myelocytes and occasional megakaryocytes are recognized. Plasma cells are present in moderate numbers. A few cells with round pyknotic nuclei and no cytoplasm are seen which may represent normoblasts, but their identification is uncertain.

Sternum. The picture is essentially similar. Evidence of proliferation is scant but there is marked fibrosis of the marrow and aplasia of both myeloid and erythroblastic elements, the latter being most markedly affected.

Although it seemed unlikely that this was a metabolic disease, investigation of the calcium and phosphorus metabolism was done. These results were normal as compared with studies on normal individuals by Bauer, Albright and Aub.

TABLE 1.—CALCIUM AND PHOSPHORUS METABOLISM.

	Period 1 (3 days). Mg.	Period 2 (2 days). Mg.
Calcium intake	279.0	186.0
Phosphorus intake	1911.0	1274.0
Urine, calcium	123.0	107.0
Feces, calcium	436.0	505.0
Urine, phosphorus	1709.0	797.0
Feces, phosphorus	447.0	526.0
Serum, calcium	10.9	9.7
Serum, phosphorus	4.0	4.1

Between May 6 and September 27, 1930, the patient spent all but 4 weeks in August in the hospital. His general condition improved and the blood level was maintained about 2,000,000 by five direct transfusions of 500 cc. at intervals of 3 to 4 weeks.

From October, 1930, to March, 1932, he has been closely followed by Dr. C. W. Heath, in the Thorndike Memorial Laboratory of the Boston City Hospital. Trial periods with a low calcium diet combined with ammonium chlorid and Lilly's liver extract, 343 (the daily equivalent of 300 gm. liver), combined with a high calcium and later a high phosphorus diet produced no remarkable change.

On October 30, 1930, he was given 0.9 cc. of adrenalin intramuscularly. In 15 minutes the red blood cells increased from 2,400,000 to 2,600,000; the white blood cells from 4100 to 19,000 and reticulocytes from 4 to 8.2 per cent and the myelocytes from 1 to 4 per cent. At the end of 5 hours the entire formula had returned to approximately the first figures.

By November 9, 1931, (when he was readmitted) the anemia had slowly advanced to 900,000 red blood cells, with a hemoglobin of 13 per cent (Sahli). The white cells numbered 15,000, showing numerous myelocytes and myeloblasts. Reticulocytes ranged from 7 to 9 per cent. While in the hospital he was given Fowler's solution for 13 consecutive days, reaching a dose of 28 minims daily. There was no objective change until 12 days after the last dose, when, with red blood cells 600,000, he developed air hunger. Two citrate transfusions were then given 1 week apart and the patient gained strength rapidly so that he was able to leave the hospital the second week after this incident. Coincident with the rise in red blood cells to 1,400,000, the white blood cell formula returned to the previous level.

Roentgenograms of the skeleton taken at this time showed no change from those taken 14 months earlier.

When last seen, September 15, 1932, the severe anemia was still present, but he was able to be up and about the house.

Case 2.—A Scandinavian stone cutter, aged 54 years, entered the hospital on March 7, 1931, complaining of weakness and anemia of 10 months' duration. He had been quite well until the preceding June, when he noted pallor and easy fatigability. In November, 1930, weakness and dyspnea on exertion forced him to stop work and on his local physician's advice he took 3 vials of a liver extract daily for several weeks but without relief.

The *family history* was noncontributory and he had 1 healthy son. In the *past* he had typhoid fever at 25 years, but gave no history of rheumatic fever, nor did he remember breaking any bones. His occupation for 30 years had been cutting granite paving blocks with a short-handled, pneumatic "plug drill." This work was in the open without protection against the moderate amount of granite dust. There was no exposure to lead or benzol.

Physical Examination. He was a well-developed, pale, gaunt man in no distress. The skin and mucous membranes were pale, with scattered petechiæ over the trunk and in the nail beds and conjunctivæ. The head and chest showed nothing unusual, except for a heart that was enlarged 10 cm. to the left in the fifth interspace and 5 cm. to the right in the fourth. The sounds were of rapid, regular rhythm with low pitched, systolic and diastolic murmurs along the left sternal margin, heard in the recumbent position. Blood pressure was 130 systolic and 58 diastolic. The pulses were equal and synchronous with poorly sustained tension. Examination of the fundi showed multiple, minute hemorrhages in the retina. The liver dullness extended from the right fifth rib to the costal margin and the spleen edge was felt 3 cm. below the left midcostal margin. The prostate, extremities and reflexes were normal.

Laboratory Examinations. Urine: normal; no Bence-Jones protein. *Blood:* red blood cells, 1,200,000; hemoglobin, 35 per cent; white blood cells, 3600 (polymorphonuclears, 65; lymphocytes, 11; mononuclears, 3; basophils, 5; myelocytes, 14; myeloblasts, 2 per cent); the smear showed marked polychromasia with variation in the size and shape of the red cells (the number of platelets was reduced); average diameter of red blood cells, 6.8 micra (dried smear); icteric index, 2; fragility of red blood cells, normal (B.H., 0.44 per cent; C.H., 0.34 per cent). Serum calcium, 8.9 mg.; serum phosphorus, 4.7 mg. Hinton test negative.

Gastric analysis with ergamin showed no free acid in 3 specimens. *Roentgenograms* of the lungs showed an old fracture of the ninth rib and changes consistent with mild silicosis. The heart was grossly enlarged to the right and left, predominantly in the region of the ventricles. The long bones were denser than normal and the medullary cavity definitely narrowed. The bone trabeculæ were dense and closely packed.

Course. Following the above roentgenologic report, a bone marrow biopsy was done and the diagnosis of osteosclerotic anemia established.

Sternum. Microscopic examination shows numerous rather thick, closely spaced bony trabeculæ. The intertrabecular spaces are occupied by dense fibrous tissue in which very rare scattered myeloblastic and hematopoietic cells are seen. There are scattered, ill-defined, multinucleated cells which are probably megakaryocytes. The findings are essentially similar to those of Case 1, the changes being slightly more marked.

The patient did not respond to liver and iron therapy and a low grade afternoon fever persisted while at rest in bed. Scattered petechiæ continued to appear, but four blood cultures gave no growth. After two transfusions, 2 weeks apart, there was marked subjective improvement and he was discharged with red blood cells 2,100,000 per c.mm.

On July 5, 3 months later, he returned in much the same state as at first. In the interval he had followed instructions by taking 12 gm. of iron and ammonium citrate daily and had received three transfusions at his local hospital. All examinations were essentially as before except that the heart was decreased in size and the diastolic murmur had disappeared. The opinion was that this was an anemia heart without valvular disease. Reticulocytes and immature white cells varied from 4 to 5 per cent. Intravenous and intramuscular aqueous liver extracts did not increase the red blood cell count above 2,100,000. A transfusion of 500 cc. was followed in 3 days by another of 250 cc., but for the remaining 6 weeks in the hospital he maintained the same low count.

Biopsy: Microscopic examination on bone marrow removed from the site of the original biopsy 6 months before shows a markedly different appearance. Bone trabeculæ are still abnormally numerous and thick. There is a tendency to callous formation. The intertrabecular spaces are no longer occupied with cellular fibrous tissue but are so closely packed with cells that identification is difficult. The predominant cells are multinucleated osteoclasts. The remaining marrow is more fibrous than normal and contains many young, apparently proliferating fibroblasts. Packed in the interstices are clusters of stem cells and masses of myeloid elements, the eosinophilic myelocytes predominating. Transition forms between stem cells and mature red cells are almost wholly lacking.

On marrow removed from an adjoining area an estimation of the silica content by King's method gave the results shown in Table 2.

TABLE 2.—SILICA CONTENT OF BONE MARROW.

	Mg. of SiO_2 per gm. of dried marrow.
Case 2	1.3
	1.2 (0.25 gm. dried marrow)
Normal	0.7
	0.4

Following this the patient was discharged home, subjectively improved but maintaining the same grade of anemia. When last heard from, on July 29, 1932, his status was unchanged and he was confined to a chair and bed life.

Comment. This type of osteosclerosis, termed myelosclerosis by Mozer, has been described in association with leukemia and with aleukemic or aplastic anemias. In 1879, in a young man dying of myeloid leukemia, Hueck found that the bone marrow was fibrous and traversed by a fine network of bony trabeculations. Schmorl, Sternberg and Mozer added like instances and Goodall described a case in an infant.

In a case without leukemia showing similar pathologic changes Askanazy demonstrated hemopoiesis within the widened capillaries of the liver and spleen. Since then in 14 cases* of myelosclerosis without leukemia, 11† showed evidence of compensatory myeloid metaplasia in the spleen. In 2 of the 11 cases[18,24] death followed splenectomy. In all probability the enlarged liver and spleen in the 2 cases I have reported harbor active hemopoiesis. In the first case the adrenalin effect was interpreted as the result of shrinkage of a spleen rich in immature blood.

In many of the cases reviewed the diagnosis of aleukemic leukemia had been made because of the immaturity of the blood cells. Such immaturity is consistently reflected in these 2 additional cases by the decreased diameter of the red blood cells, the reticulated forms and the frequent myelocytes. Rather than a leukemic process, this appears to be the continued hurried response of an insufficient number of marrow cells. In both cases the red blood cells could not be maintained above 2,500,000. It seems that the maximum output of the reduced marrow tissue was equivalent only to this low level.

The future of these patients is quite uncertain, although it is known that Jores' patient lived as long as 8 years with the disease.

This type of osteosclerosis appears to be a response to injury rather than a metabolic disease, as is likely in marble bones. Subacute bacterial endocarditis was considered in the second case particularly because of the previous observation[17] of the coëxistence of these diseases. Similar but local reactive processes such as osteoplastic cancer metastases, "spotted bones,"[2] radiation osteitis[15] and periosteitis and sclerosis associated with phosphorus poisoning[26] were excluded. It is of some interest that marrow sclerosis has been produced in animals by strontium feeding[14] and by intravenous saponin.[6]

In these 2 cases there was a prolonged exposure to silica dust. No such exposure could be determined from the histories of the cases

* See Bibliography, Nos. 4, 7, 9, 11, 16, 17, 18, 21, 24, 25, 28.
† See Bibliography, Nos. 4, 7, 9, 11, 16, 17, 18, 24, 28.

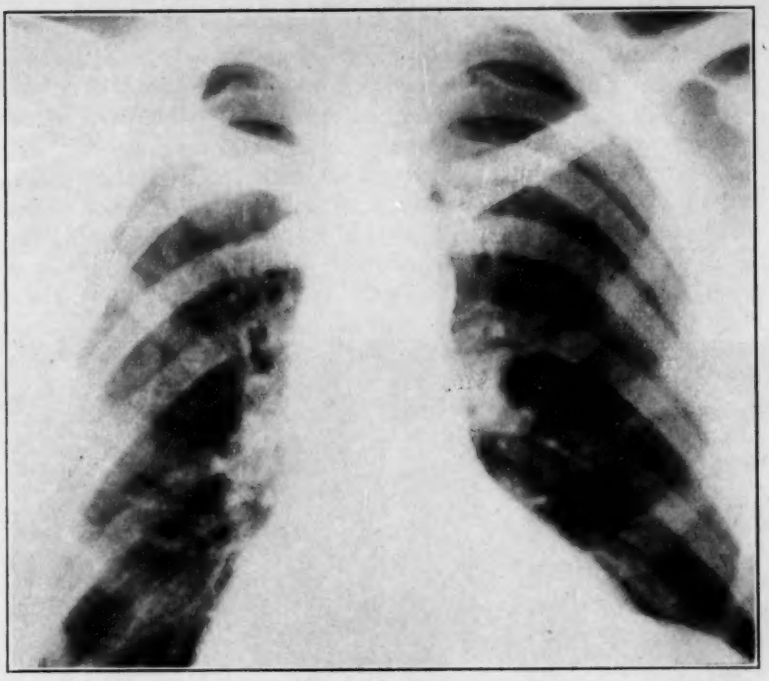


FIG. 1.—Case 2. Roentgenogram of the chest, showing an old fracture of the ninth rib and changes consistent with mild silicosis.

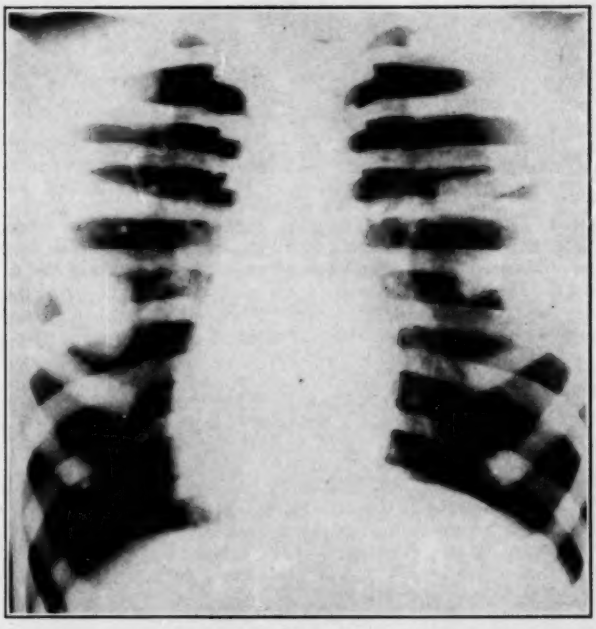
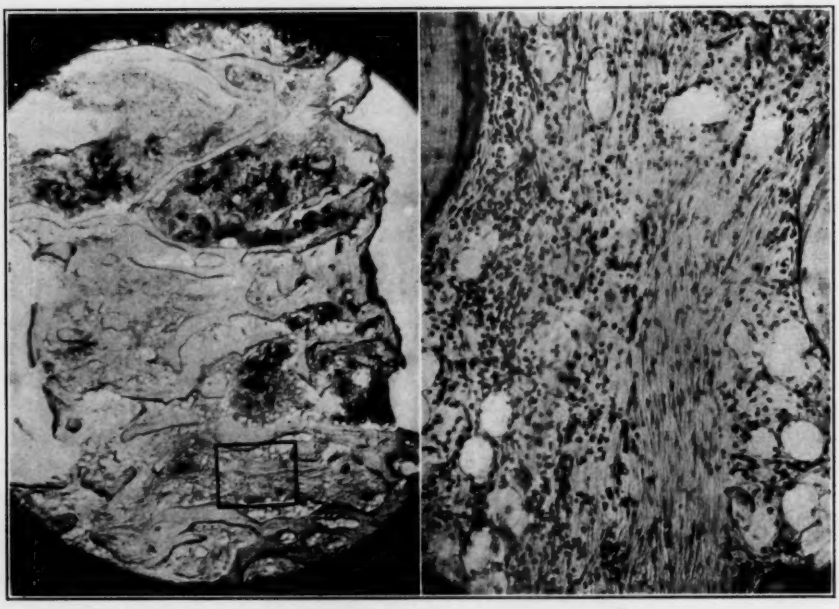


FIG. 2.—Roentgenogram of the chest of a child, aged 8 years, with marble bones. (Unpublished collection of Dr. C. N. McPeak.) Note the marked density of the bone with obliteration of the bony structure.



A *B*

FIG. 3.—Case 1. Rib biopsy. *A*, showing slight increase of trabeculæ, absence of osteoid tissue and interosseous spaces mostly filled with fatty and fibrous tissue. (× 25.) *B*, from the area indicated in *A*. Note the dense connective tissue and the scarcity of marrow cells. (× 175.)

reviewed, in most of which the origin of the disease is quite obscure. Welch has described multiple anthracotic nodules in the liver and more recently Riddell has found extrapulmonary silicosis in the liver and spleen. Although no such description has been found,* it is possible that cell ingested silica could be deposited in the marrow and there produce sclerosis. The estimations of silica in the marrow of the case with evidence of silicosis are interpreted as normal until more tissue is available. In 75 patients with moderate to advanced silicosis personally examined in Barre, Vt., in the past year none showed evidence of an osteosclerotic anemia.

Summary. 1. Two cases of unexplained osteosclerosis are presented. Fever, splenomegaly and a myelophthisic anemia with evidence in the peripheral blood of active hemopoiesis were the outstanding features.

2. The best treatment is palliative with transfusions, while splenectomy, arsenic and radiation are contraindicated.

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* Since submission for publication osteosclerosis associated with silicosis has been found in workers in cryolite. (P. F. Møller and S. V. Gadjonsson. *Acta Radiologica*, 1932, **13**, 269.) In several a moderate anemia of secondary type was present but examination of the bone marrow was not reported. In these cases the sclerosis both of ligaments and bones was attributed to the sodium fluorid present in cryolite.

NEGATIVE RESULTS OF OXYGEN THERAPY IN POLYCYTHEMIA VERA.

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Bert[1] was the first to suggest that a lowered supply of oxygen to the body resulted in an increase in the oxygen-carrying capacity of the blood (1878, 1882). That an actual polycythemia resulted from ascent to high altitudes was demonstrated in 1889 by Viault,[2] whose erythrocyte count rose from 5,000,000 to 8,000,000 cells at an altitude of 4392 meters in the Peruvian Andes. Studies by Dallwig, Kolls and Loewenhart[3] and by Campbell[4] on animals kept in low oxygen tensions but at normal barometric pressures showed that the degree of polycythemia produced was proportional to the severity of the anoxemia. Similar results were obtained in men breathing air containing low concentrations of oxygen.[5] The occurrence of varying degrees of polycythemia as a result of anoxemia in clinical disease is seen in congenital heart disease, emphysema of the lungs and in chronic carbon monoxid poisoning.

As a result of the diminished rate at which gases (oxygen and carbon monoxid) passed through the lungs in 7 tested cases of polycythemia, Harrop and Heath[6] suggested that an actual reduction in arterial blood oxygen tension might be present and might constitute the stimulus to the increased erythropoietic activity. Favorable results were claimed by Koranyi[7] and Bence[8] as a result of oxygen inhalations. Harrop[9] mentions that 3 hours of oxygen inhalation produced no change in a case of his own and refers to an unpublished case of Binger and 1 of Poulton,[10] in which no change resulted from the inhalation of 40 per cent oxygen for several days in an oxygen chamber.

The possibility that polycythemia vera might be an example of histotoxic anoxemia from an unknown poison interfering with the absorption of oxygen by the tissue cells led to a renewed trial of oxygen inhalation over a longer period of time. Barcroft, Hunt and Dufton[11] had showed that a reduction in red blood cells and hemoglobin took place after a week's exposure to 40 per cent oxygen in cases of chronic gas poisoning that had a relative poly-

cythemia. Campbell[12] and Barach[13] reported that a slight diminution in erythrocytes and hemoglobin took place in normal animals exposed to 60 per cent oxygen over longer periods of time.

Two cases were selected from the ward service and put into an oxygen chamber of the Barach[14] type for 15 days in 1 case and 17 days in the other. The oxygen concentration was maintained at 50 per cent. The temperature was between 68° and 70° F., the relative humidity 40 per cent.

The case histories and tables follow:

Case Reports. CASE 1.—R. I. (No. 326995), a Norwegian butler, aged 59 years, was admitted, January 11, 1932, complaining of shortness of breath and cramps in various parts of his body. His abdomen and legs were said to have been swollen for 5 months. He was aware of having had diabetes for 8 years. Attacks of substernal pain were sufficiently severe to suggest coronary disease. There were also cramplike pains in arms, shoulders and legs. He had attacks of dizziness and shortness of breath even when resting in bed.

On examination, the important findings were: an enlarged heart, systolic murmurs at the apex and aortic areas, with numerous premature beats. The liver edge was felt 4 cm. below the costal margin, but the spleen was never palpable. The lower extremities were edematous. Blood pressure was 160 systolic and 80 diastolic.

The blood count revealed polycythemia; red blood cells, 7,940,000 to 11,270,000; hemoglobin, 138 to 142 per cent. The urine contained both albumin and sugar. An electrocardiogram showed evidence of myocardial damage and fairly numerous extrasystoles. Roentgen ray of the gastrointestinal tract showed no evidence of organic disease.

The cramplike pains were the most annoying symptom. Nitroglycerin helped slightly but rarely afforded complete relief.

TABLE 1.—RESULTS IN CASE 1 BEFORE AND AFTER 17 DAYS' RESIDENCE IN A CHAMBER CONTAINING 50 PER CENT OXYGEN.

Date, 1932.	Hgb.	R.b.c.	W.b.c.	Polys.	Arterial oxygen content.	Oxygen capacity.	Arterial oxygen saturation.	Remarks.
Jan. 11	138	7,940,000	8,400	79				
13	142	11,270,000						
14	142	8,760,000	7,120	77				
15	..	..	..	..	..	..	..	Phlebotomy, 500 cc.
18	132	9,800,000	9,900	78				
27	145	9,500,000	9,300	81				Phenylhydrazin, 2 gm.;
29	142	9,100,000	10,000	79	..	..	..	2 days.
Feb. 1	140	9,300,000						
4	138	8,100,000	10,800	80	..	..	..	Phenylhydrazin, 2 gm.; 2 days.
8	130	9,600,000						
10	129	8,400,000						
15	130	8,300,000	7,400	84	..	..	..	Entered oxygen chamber.
17	..	..	..	..	25.5	26.5	96.3	
23	130	8,200,000	10,400	80				
29	120	8,000,000	9,500	83				
Mar. 2	..	..	..	..	24.5	24.9	98.4	
4	126	7,500,000	..	..	..	..	..	Left oxygen chamber.

He was given a little phenylhydrazin hydrochlorid (0.8 gm. in 10 days) with no apparent benefit. He was put in the oxygen chamber, where he remained for 17 days. The cramplike pains were markedly diminished

in frequency and severity during the first 24 hours, and, although they recurred from time to time, were never as troublesome as before admission to the oxygen chamber.

The erythrocyte count, hemoglobin percentage and oxygen capacity are seen in Table 1 to be uninfluenced by residence in an oxygen-rich atmosphere. The arterial oxygen saturation was slightly increased when he was breathing 50 per cent oxygen.

CASE 2.—T. B. (No. 329295), a man, aged 48 years, entered the ward with a 6-month's history of noises in head, dizziness and shortness of breath. Two years before admission he had vomited blood several times. Headaches were annoying at this time but improved as he lost weight. During the past 2 years his weight had dropped from 230 to 173 pounds.

He had received two courses of treatment with phenylhydrazin 9 months before admission (2 gm. in 2 months). Three months before admission he had taken 1.6 gm. in 2 weeks. The red cells dropped from 11,000,000 to 7,700,000 but subjective improvement was not marked.

When admitted, the patient was a large, plethoric and cyanotic Italian, apparently chronically ill. The heart was enlarged, but the sounds were of good quality and no murmurs were heard. The blood pressure was 110 systolic and 70 diastolic. The right lung was apparently normal. At the left base there was slight dullness, with diminished voice and breath sounds. The spleen was felt 4 cm. below costal margin. The liver was not palpable. In the left upper quadrant there was a large, freely movable, nontender mass, approximately 10 cm. in diameter. This was thought to be kidney but Roentgen ray threw no light on the subject and its actual nature remained in doubt.

The patient was placed in the oxygen chamber for 15 days with little change in symptoms or blood count. The arterial oxygen saturation was very slightly below the usual normal range before he entered the chamber. It increased from 93.2 to 98.3 in 50 per cent oxygen.

One month later he seemed to feel a little better and the red cells were a trifle lower.

TABLE 2.—RESULTS IN CASE 2 BEFORE AND AFTER 15 DAYS' RESIDENCE IN A CHAMBER CONTAINING 50 PER CENT OXYGEN.

Date.	Hgb.	R.b.c.	W.b.c.	Polys.	Arterial oxygen content, vol. %.	Oxygen capacity, vol. %.	Arterial oxygen saturation, vol. %.	Remarks.
Feb. 10	115	8,000,000						
14	125	7,550,000	17,400	95				
16	127	10,300,000	22,300	82	23.1	24.8	93.2	
17	..	..	..	..	..	..	..	Entered oxygen chamber.
23	135	9,500,000	17,200	84				
29	122	9,000,000	17,300	84				
Mar. 1	..	..	..	..	23.5	23.9	98.3	
4	122	8,700,000	..	..	..	..	..	Left oxygen chamber.
29	115	8,200,000	29,600	85				

Summary. No significant alteration in the red blood cell count, the hemoglobin percentage or the oxygen capacity took place in either of 2 cases of polycythemia vera who breathed an atmosphere containing 50 per cent oxygen for a period exceeding 2 weeks. This appears to make improbable the theory that polycythemia vera is based on an anoxemic stimulus. The relief of the cramp-

like pains in 1 case seemed due to an alleviation of a condition of local anoxemia associated with the presence of an increased number of red cells and a consequent locally retarded blood flow. In each of the cases there was a slight increase in the arterial oxygen saturation while the patients were breathing 50 per cent oxygen in the chamber.

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ANEMIA IN AZOTEMIA.*

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Anemia is common in chronic nephritis. Richard Bright[1] observed its development in the course of the disease, remarking, "After a time the healthy colour of the countenance fades." That anemia may occur in various renal lesions other than chronic glomerular nephritis, such as nephrosclerosis, polycystic kidneys, failure of one kidney following the surgical removal of the other, and in renal damage resulting from urinary retention due to hypertrophy of the prostate, is less commonly recognized. From a review of the liter-

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ature and case studies we shall show the parallelism that exists between the anemia and the nitrogen retention (azotemia), not only in chronic Bright's disease, but in other pathologic renal conditions.

Robert Christison[2] was among the first to make accurate analysis of the blood in chronic nephritis. He well understood the grave prognostic significance of the gradually developing anemia, stating, ". . . the proportion of the hematosin in the blood has appeared to me to constitute under certain conditions one of the surest criterions of the progress which the organic derangement has made in the structure of the kidneys, and therefore to be one of the most useful symptoms which a physician can attend to in a practical point of view" (loc. cit., p. 31). The "hematosin," or "the coloring matter" of the blood was determined by allowing the corpuscles to settle out in a weighed sample of defibrinated blood and determining their dry weight in proportion to the total weight of the original sample of blood. The amount of hematosin in healthy adults varied, according to Christison, from 1160 to 1535 parts per 10,000 of blood. From a table (p. 35) in which are recorded 10 cases of "granular kidney," the amount of hematosin varied from 1339 (normal) to as low as 427, with an average of 905.3 parts per 10,000 parts of blood, or about 67 per cent of the normal figure (obtained by averaging 1160 and 1535, given above).

In 1850, Schmidt,[3] studying the blood of cholera patients, also included in his report several (loc. cit., pp. 111, 121, 127) cases of nephritis. He found in them a marked decrease in the volume of the cells in proportion to the plasma. An example (p. 127) was a man aged 39 years, with chronic nephritis and marked edema. The blood contained 34.2 per cent cells and 65.7 per cent plasma by volume—a considerable degree of anemia. In 1878, Leichtenstern[4] demonstrated a reduction in the amount of hemoglobin in Bright's disease. He studied the blood in 3 chronic cases and found that the hemoglobin content was ". . . appreciably reduced, in a high degree particularly in a case of 'granular atrophy' of the kidneys with a waxy-yellow appearance of the patient" (p. 88; also Table 19, pp. 90, 91). In this case the hemoglobin was 9.22 gm. per 100 cc. of blood (by calculation based on spectrophotometric figures in the text).

The cause of the anemia in azotemia is still unknown. In 1905, Ceconi[5] made careful studies on the blood in 25 cases of nephritis. He found no increase in the fragility of the erythrocytes, but rather, in general, a tendency to an increased resistance. This he attributed to some retained toxic substance which rendered the union between the hemoglobin and the erythrocyte more tenacious. He concluded that the anemia in chronic nephritis was not due to increased red cell destruction, but rather to a deficiency in the hematopoietic system, which was probably caused by a paralyzing action of retained poisons.

Grawitz[6] was of the opinion that the blood plasma became richer in water, that is, hydremic. He recognized two stages in the course of chronic nephritis. First, a stage of adequate cardiac function with no alteration in concentration or number of erythrocytes in the circulating blood; later, a stage of inadequate cardiac function due to weakening of the hypertrophied left ventricle of the heart. In this stage he said, ". . . there is a progressive thinning of the blood due to the increase in water . . ." leading to ". . . abnormally lowered values for the blood corpuscles and hemoglobin."

This dilution theory has been disproved by the work of Keith, Rowntree and Geraghty[7] in 1915. Studying the relationship of the plasma volume to the total blood volume they found that the latter constitutes 1/11.4 of the body weight and that the former varies from 42 to 56 cc. ker kg. of body weight. They also observed that the plasma volume was not increased in chronic nephritis. This work has been confirmed by Bock.[8] He found that the blood plasma constitutes 5.1 per cent or 1/19.6 of the body weight, and that it remains remarkably constant both in health and disease. In cases of edema in cardiac and renal disease he found the plasma volume remained constant.

From the observations of these workers it is evident that no increase in total plasma volume occurs in chronic nephritis. Therefore, the anemia which is usually present in the advanced stage of the disease is not due to simple dilution of the corpuscles, but rather to an absolute decrease in their number.

Fundamentally, there are three types of anemia: (1) Anemia due to deficient blood formation; (2) anemia due to excessive blood destruction, and (3) anemia due to blood loss. The amount of blood lost in the urine in chronic nephritis is probably too small to account for the anemia. Brown and Roth[9] found that in 89 cases of chronic nephritis with anemia, 34 (38 per cent) showed no erythrocytes in the urine, although the hemoglobin averaged 59 per cent and the erythrocytes 3.01 millions per c.mm. of blood. Furthermore, no relationship was found to exist between the amount of blood in the urine (excluding its presence macroscopically) and the degree of anemia. For example, 4 cases, with sufficiently large amounts of blood to be almost macroscopic, had an average hemoglobin of 57 per cent and erythrocyte count of 2.95 millions, while 39 with almost no blood microscopically visible had averages of 54.7 per cent hemoglobin and 3.31 millions erythrocytes.

The problem of the rôle of excessive destruction of blood in the body in the pathogenesis of anemia in chronic nephritis is not so easily settled. Clark and Evans[10] showed that the serum of patients having pernicious anemia exhibits a decrease in its protective antihemolytic property. Experiments were conducted *in vitro*, using guinea-pig erythrocytes and sodium oleate for the hemolytic agent. A marked decrease in protective antihemolytic power of pernicious

anemia serum as compared with serum from normal subjects and those suffering from a wide range of diseases without anemia was observed. While some reduction in protective power of the serum was observed in various other types of anemia, it was much less than in pernicious anemia.

Brown and Roth[9] tested the protective value of the blood serum against hemolysis of homologous erythrocytes by hypotonic salt solution and found that the protective property of human serum is fairly constant in both normal persons and those suffering from chronic nephritis, either with or without anemia.

The chief underlying factor in the pathogenesis of anemia in chronic nephritis is probably defective blood formation. The appearance of the erythrocytes in stained smears lends support to this hypothesis. Anisocytosis, poikilocytosis, polychromasia and hypochromasia were not at all marked in the slides of our cases. Nor was the color index very low as in other secondary anemias (Table 3). Brown and Roth[9] found no increase in the reticulocytes in a number of their cases, even though the anemia was quite severe. While most writers refer to the anemia in chronic nephritis as "secondary," it is not markedly hypochromic. In fact, there seems to be an element of aplasia of the marrow involved. More careful studies of the bone marrow are needed in this field.

Some authors have reported examples, in their opinion, of hyperchromic anemia in chronic nephritis. Berg[11] observed that in 7 of his 12 cases (Table 1) of chronic nephritis with nitrogen retention the color index was 1 or slightly above, as 1.1. From a study of our cases (Table 3) we have found a similar circumstance, but we do not regard it as evidence of hyperchromia but rather of a high normal reading. For routine work we use the new Sahli hemoglobinometer, carefully checked against the Bausch & Lomb Company's Newcomer type instrument. The latter has been very carefully calibrated by us, using the O_2 and CO_2 combining power methods. Only very slight readjustment was found necessary. An average color index of 1.31 has been found in 76 cases of pernicious anemia carefully studied by us in the hematology laboratory since August, 1930. In normal individuals we usually find the color index 0.9 to 1.

The enumeration and morphology of the leukocytes in the anemia of chronic nephritis have been insufficiently studied. In 20 of our cases, including 1 of polycystic kidneys, we found an average white cell count of 13,839, which is considerably higher than the average of 9020 in the 105 cases reported by Brown and Roth.[9] We frequently observed a moderate shift to the left in the neutrophils in our cases, but this may have been due to terminal complicating infections which, in turn, may be the reason we so commonly found a mild leukocytosis.

Kollert and Paschkis[12] observed that infections complicating nephritis, as sinusitis, tonsillitis, endocarditis and otitis media, pro-

duced an alteration in the leukocytic picture with a leukocytosis and a shift to the left in the neutrophils. These changes coincided with an increase in the sedimentation rate of the erythrocytes. Schilling[13] states that there is little or no shift in uncomplicated cases of chronic nephritis.

The blood platelets in some cases of chronic nephritis are reduced in number. Brown and Roth[9] found an average of 152,000 per c.mm. in 8 of their cases. "A condition," they remarked, "which may have some bearing on the hemorrhagic tendency in some of the more severe cases of chronic nephritis with anemia." We have not found a material reduction in their number in our cases. In fact, Case 16 (Table 3) is that of a young woman having very severe bleeding from the gums, which was the outstanding clinical feature until further study proved the existence of chronic nephritis, and yet the platelet count was 274,000. Case 21 was very similar, but unfortunately no platelet count was made.

The relationship of nitrogen retention to anemia is very important. From a review of the literature it appears that the anemia is not limited to cases where the retention is due to chronic nephritis, but is also seen in azotemia due to other lesions, as congenital polycystic kidneys, arteriosclerotic renal disease, surgical removal of one kidney with failure of the other, and in urinary retention due to hypertrophy of the prostate.

Aubertin and Yacoel[14] in their article, presented a table (p. 462) which included 11 cases of chronic nephritis with azotemia and 6 cases without azotemia. The average total nonprotein nitrogen (our calculation) in the azotemic group was 244 mg. per 100 cc. of blood; the average number of erythrocytes, 2.46 millions per c.mm. In the nonazotemic group the nonprotein nitrogen averaged 43 mg. and the erythrocytes 3.66 millions. They concluded that in nephritis with azotemia there is a severe anemia, while those cases without nitrogen retention showed an insignificant anemia. Berg,[11,15] in 1922, in a study of 28 cases of nephritis, 12 of them with nitrogen retention ranging from 43 to 214 mg. of urea per 100 cc. of blood, found that severe anemia in chronic nephritis is seen chiefly in cases with nitrogen retention. However, 1 of his cases with only 50 mg. of urea had 1,504,000 red blood cells, while another with 121.8 mg. of urea had a red count of 4,180,000. Brown and Roth[9] in the same year, in an analysis of 187 cases of chronic nephritis, of which 105 had anemia, concluded that anemia was not proved to be due to an increase of nitrogenous substances in the blood, although if severe, had the same prognostic significance as creatinin retention. They observed that hemoglobin values of 60 per cent or less have approximately the same serious prognostic significance as creatinin values of 5 mg. and above, over a $2\frac{1}{2}$-year period. The same workers[16] in the following year published a report on the prognostic value of anemia in chronic nephritis. Twenty of their cases had an average

hemoglobin of 48.5 per cent (Dare) and 2,950,000 red cells with creatinin of 5 mg. or above. Nineteen of these 20 died within 10 months of the time of first observation.

In 1924 Aubertin and Yacoel,[17] from a study of 14 cases of chronic nephritis with nitrogen retention, concluded that the anemia that so often occurs in these cases is usually progressive and parallel to the azotemia. From our analysis of their cases we find that the average nonprotein nitrogen values in the blood were 185 mg. per 100 cc. of blood, and the red cell count 2.5 millions per c.mm. In studying the blood in cases of hypertension, Adams and Brown[18] have observed that 56 cases with adequate renal function (normal urea and creatinin) had an average hemoglobin of 106 per cent and an erythrocyte count of 4,670,000. In the same study 20 cases with impaired renal function (nonprotein nitrogen above 50 and creatinin above 2.5) had an average hemoglobin of 81 per cent with 3,870,000 red cells. They stated that, "The anemia in cases of hypertension is not as marked as that observed in cases of glomerulonephritis." Furthermore, "Renal insufficiency can be recognized by the onset of anemia in cases of hypertension." The high normal and increased erythrocyte count in cases of hypertension has been designated by Geisböck[19] as "polycythemia hypertonica." It is apparently not due to alterations of the blood volume or plasma volume, but may be due to compensatory erythropoiesis due to diminished oxygenation from varying degrees of cardiac insufficiency.

Scarlett,[20] in 1929, analyzed 51 cases of chronic nephritis and found as averages: erythrocytes, 2,780,000; hemoglobin, 51 per cent; color index, 0.9; urea nitrogen, 86.3 mg.; and creatinin, 9.3 mg. per 100 cc. of blood respectively. He agreed with the findings of other observers that the presence of a severe anemia in chronic glomerular nephritis has practically the same prognostic value as blood creatinin of 5 mg. or over. He also reported 4 cases of chronic glomerular nephritis with uremia without hypertension, cardiac hypertrophy or retinal changes, in which anemia was the only clinical finding. Three of these died within a year from the time first seen. All had increased blood nitrogen and a severe secondary anemia.

Ashe,[21] in an excellent review of 300 cases of Bright's disease, myocardial insufficiency, hypertension, polycystic kidneys and surgical removal of one kidney, concluded that a secondary anemia is always present in renal insufficiency from any cause and is directly proportional to the degree of insufficiency. While the blood chemistry and renal function dye excretion tests are largely absent it is obvious from his study that the cases which he designated as showing "marked and maximal renal insufficiency" showed a definite anemia of the secondary type. Among this class 40 cases diagnosed by him as chronic diffuse nephritis showed an average hemoglobin of 54 per cent; red cells, 2,944,000, and a color index of 0.92. Those of renal insufficiency accompanying hypertension with maximal renal impair-

ment showed an average hemoglobin of 65 per cent; average red cells, 3,775,000, and a color index of 0.87. His study of 3 cases of polycystic kidney is valuable, although here again specific values for the blood chemical constituent and dye excretion tests are lacking. The first case showed a hemoglobin of 80 per cent and 4,256,000 red cells, and was classed as having moderately impaired renal function. The other 2 cases showed a hemoglobin of 44 per cent and 55 per cent and 2,728,000 and 3,900,000 red cells, respectively. These were designated as having maximal renal insufficiency. Two examples were also given of surgical removal of one kidney, one with no impairment of renal function with a hemoglobin of 80 to 90 per cent, the other with maximal renal insufficiency with a hemoglobin of 45 to 56 per cent and 2,500,000 to 3,882,000 red cells.

Van Slyke[22] is in agreement with many others that the prognostic value of anemia is usually of the same weight as the increase in blood urea. He stated that although anemia is practically always present in the terminal stage of chronic nephritis, the absence of a low hemoglobin does not mean that uremia will not ensue. He found that anemia was present in arteriosclerotic Bright's disease in 5 out of 6 cases studied, but "to a less extensive degree than in the terminal cases of hemorrhagic nephritis" (glomerulonephritis). Further, that "anemia likewise is by no means uniformly absent in nephrosis." Out of 10 cases only 3 showed hemoglobin above 80 per cent. Also that "a blood hemoglobin content was also followed, and although of not decisive diagnostic value was found to be of interest as an indication of the toxic damage suffered by the organism, and to have prognostic significance."

Klemperer and Otani,[23] in a comprehensive study of 16 cases of nephrosclerosis, happily included hemoglobin and erythrocyte estimations of nearly all the cases. Excluding Case 1, a male, aged 29 years, blood pressure 230 systolic and 172 diastolic, with the urea 14 mg. and hemoglobin 102 per cent, 4,800,000 red cells, and Cases 5, 7 and 10, in which no record of blood counts or hemoglobin is given, we find the following averages: Urea, 84.5; hemoglobin, 53 per cent; 3,055,000 red cells; color index, 0.88. Lowest urea, 29; hemoglobin, 50 per cent; highest urea, 190; hemoglobin, 39 per cent. Lowest hemoglobin, 35 per cent; urea, 45; highest hemoglobin, 70 per cent; urea, 63. Lowest red cells, 1,250,000; urea, 45. Highest red cells, 4,600,000; urea, 63. From these last figures it is at once obvious that the functional status of the hematopoietic system varies markedly in individual cases and is not an exact indication of the degree of nitrogen retention. On the other hand, the average case with urea 84.5 had a definite secondary anemia.

In Table 1 we have summarized the figures of the various authors, including ourselves, who have reported series of cases presenting anemia with azotemia. It can be seen at a glance that there is a definite anemia in all the series. Unfortunately, it is impossible

accurately to compare the blood chemistry findings with these, since some authors have reported total nonprotein nitrogen values, others the urea, others creatinin, and one author stated that there was marked and maximal renal impairment without reporting the blood chemistry findings.

TABLE 1.—ANEMIA IN NITROGEN RETENTION (AVERAGE FIGURES IN LITERATURE).

Author.	Year.	No. of cases.	Blood chemistry.	Hb., per cent.	Erythrocytes, millions.	Color index.	Condition.
Aubertin and Yacoel[14]	1920	12	N.P.N. 220	35	1.100	1.6	Nephrosclerosis
Berg[15]	1922	12	Urea 92.5	47	2.550	0.93	Chronic nephritis
Brown and Roth[16]	1922	20	Creatinin 8.8	48	2.950	0.82	Chr. glom. nephritis
Aubertin and Yacoel[17]	1924	18	N.P.N. 112	..	3.270	..	Chronic nephritis
Adams and Brown[18]	1925	20	N.P.N. (?) over 50	81	3.870	1.0	Hypertension with impaired renal function
Scarlett[20]	1929	51	Urea 86.3	51	2.780	0.90	Chronic nephritis
Ashe[21]	1929	10	*	54	2.940	0.92	Chr. diffuse nephritis
Ashe	1929	18	*	65	3.377	0.87	Hypertension with impaired renal function
Ashe	1929	2	*	49	3.310	0.74	Polycystic kidneys
Ashe	1929	1	*	50	3.190	0.80	Surg. remov. of 1 kidn.
Klemperer[23]	1931	15	Urea 84.5	53	3.055	0.88	Malig. nephrosclerosis
Parsons and Ekola-Strolberg	1931	2	N.P.N. 250 Creatinin 6.5	53	2.390†	1.0†	Congenital polycystic kidneys
		2	N.P.N. 176 Creatinin 5.6	53	3.265	0.93	Acute nephritis
		4	N.P.N. 218 Creatinin 9	55	2.672	0.94	Nephrosclerosis
		13	N.P.N. 193 Creatinin 8.3	50.7	2.578	0.99	Chr. glom. nephritis

* Marked and maximal renal impairment. † One case only.

TABLE 2.—NORMAL CREATININ VALUES BELOW 5 MG. PER 100 CC. OF BLOOD.

Number.	Laboratory number.	Age.	Sex.	Renal lesion.	Duration of symptoms.	Nonprotein nitrogen.	Creatinin (mg. per 100 cc.).	Erythrocytes (millions).	Hemoglobin (per cent).	Color index.	Leukocytes.	Platelets (thousands).
1	H-210	63	M	Nephrosclerosis	2 mos.	40	1.3	3.89	77	1.0	8,350	
2	H-245	31	M	Amyloid nephr.	1 yr., 4 mos.	30	1.5	4.90	96	0.98	10,950	
3	H-264	28	M	Acute nephr.	2 mos.	41	1.5	3.76	84	1.12	17,800	328
4	H-287	72	M	Prostatism	.....	60	1.5	5.11	97	0.95	25,150	152
5	H-275	51	M	Chr. glom. neph.	.....	80	1.5	3.95	83	1.05	9,600	294
6	H-670	13	F	Subacute glom. neph.	8 mos.	50	1.6	2.42	37	0.77	7,000	370
7	H-323	60	M	Embolic neph.	Few weeks	82	1.7	5.00	108	1.08	7,850	172
8	H-208	40	F	Pyelonephritis	2 mos.	29	1.8	3.54	71	1.0	14,550	144
9	H-495	69	M	Arteriosel. neph.	3 wks.	78	2.0	4.89	89	0.92	7,250	200
10	H-558	42	M	Bilat. ren. calc. w. pyeloneph.*	1mo. with N.P.N. above 50	85	2.1	4.97	99	1.01	15,650	236
11	H-219	37	M	Chr. glom. neph.	1 yr., 3 mos.	96	2.1	6.25	116	0.93	14,550	220
12	H-553	55	F	Bilat. ren. calc. w. pyeloneph.*	1 wk. with N.P.N. above 40	133	2.3	4.65	91	0.97	37,600	
13	H-405	85	M	Prostatism	Few days	109	2.4	4.76	91	0.96	11,650	190
14	H-384	20	F	Nephrosclerosis	10 mos.	150	2.6	2.57	43	0.86	9,950	434
15	H-506	27	M	Prob. nephrosel.	1 yr. intermit.	125	3.0	3.69	80	1.1	9,950	178
16	Autop. 2426	44	M	Chr. glom. neph.	3 mos.	120	3.0	3.80	70	0.92	13,050	
17	H-502	35	M	Chr. glom. neph.	4 yrs. intermit.	100	3.2	3.24	69	1.07	6,150	216
18	Autop. 4951	78	M	Arteriosel. neph. ren. cal.†	N. retention about 6 mos.	133	3.3	4.60	95	1.03	8,900	
19	H-475	56	M	Malig. nephrosc.	3 mos.	98	3.5	2.90	63	1.08	10,450	203
20	H-507	67	M	Nephrosclerosis	2 yrs.	133	4.0	2.77	59	1.09	11,750	135
21	H-649	62	M	R. pyonephrosis, l. kidney out.	3 yrs.	150	4.7	2.10	42	1.0	4,550	250
		..	..		.....							
Averages:							2.4	3.99	74	0.95	11,385	

* Bilateral renal calculi with pyelonephritis. † Arteriosclerotic nephritis with renal calculi.

In Table 2 we have listed 21 cases of different types of renal lesions having creatinin values ranging from normal to 4.7 mg. per 100 cc. of blood. In only 2 of these was the creatinin above 3.5 mg., although the nonprotein nitrogen showed figures as high as 150 mg. The average creatinin was 2.4 mg.; erythrocytes, 3,988,000; hemoglobin 74 per cent, and the color index, 0.95.

In Table 3 are 21 examples of renal lesions with creatinin values ranging from 5 to 12 mg. per 100 cc. of blood. These cases have been classified according to the lesion in Table 1 and the average figures for the different lesions recorded there. The average creatinin in these 21 cases is 7.6 mg.; erythrocytes, 2,570,000; hemoglobin, 52.5 per cent, and the color index, 1. It may be seen that a very considerable degree of anemia is present in these cases. Case 4 is an apparent discrepancy having a creatinin 5.3 and 4,390,000 red cells, the duration of symptoms, however, was only 15 days and it is not unlikely that, had the azotemia persisted over a longer period of time, anemia would eventually result.

TABLE 3.—CREATININ VALUES OF 5 MG. OR ABOVE PER 100 CC. OF BLOOD.

Number.	Laboratory number.	Age.	Sex.	Renal lesion.	Duration of symptoms.	Nonprotein nitrogen.	Creatinin (mg. per 100 cc.).	Erythrocytes (millions).	Hemoglobin (per cent).	Color index.	Leukocytes.	Platelets (thousands).
1	H-404	40	F	Nephrosclerosis	6 mos.	300	5.0	3.41	58	0.85	17,450	324
2	Autopsy 2262	45	F	Chr. glom. neph.	Over 1 yr.	200	5.0	2.33	50	1.0	20,000	
3	H-667	34	F	Chr. glom. neph.	4 mos.	200	5.3	3.15	62	1.0	20,900	
4	H-332	23	F	Acute nephritis	15 days	153	5.3	4.39	75	0.87	11,900	382
5	H-474	55	M	Nephrosclerosis	6 mos. (?)	162	6.0	3.23	71	1.1	15,750	152
6	Autopsy 2245	40	M	Chr. glom. neph.	2 mos.	120	6.0	2.94	70	1.2	19,200	
7	Autopsy 3850	51	F	Chr. glom. neph.	12 yrs.	143	6.0	3.50	63	0.9	8,800	
8	Autopsy 7363	42	F	Congen. cyst. kidneys	5 mos.	260	6.0	2.39	46	1.0	13,550	304
9	H-391	27	F	Acute nephritis	3 mos.	200	6.0	2.14	42	1.0	12,050	292
10	Autopsy 5086	69	F	Chr. glom. neph.	4 mos.(?)	122	6.2	2.90	40	0.68	19,000	
11	Autopsy 7417	44	M	Congen. cyst. kidneys	3 mos.	240	7.1	...	60			
12	H-222	52	M	Nephrosclerosis	1 yr.	171	7.5	1.91	37	0.97	13,150	372
13	H-221	35	M	Chr. glom. neph.	2 mos.	214	8.5	1.35	25	0.96	21,000	508
14	Autopsy 4675	48	M	Nephrosclerosis	1½ yrs.	240	8.6	2.14	..	...	5,950	
15	Autopsy 5428	40	M	Chr. glom. neph.	3 mos.(?)	200	8.6	3.00	..	...	20,400	
16	H-622	23	F	Chr. glom. neph.	2 mos.	187	9.1	1.38	26	1.00	10,250	274
17	H-465	26	M	Chr. glom. neph.	2 yrs.	184	9.3	1.92	32	0.81	7,800	
18	Autopsy 7895	52	F	Chr. glom. neph.	6 wks.	200	10.0	2.80	40	0.70	14,750	
19	Autopsy 3498	37	M	Chr. glom. neph.	1 mo.	250	10.0	3.14	90?	1.4?	10,440	
20	Autopsy 3490	46	M	Chr. glom. neph.	3 mos.	240	12.0	3.51	85	1.2	10,450	
21	Autopsy 5023	36	F	Chr. glom. neph.	1 mo.(?)	254	12.0	1.60	26	0.81	11,000	
Averages:		..	..	....	....	..	7.6	2.57	52.5	1.05	13,839	

From the series of cases reported and tabulated in Table 1, as well as from our own study, it is apparent that anemia is an almost constant accompaniment of azotemia. Whether the nitrogenous

substances retained in the blood are the cause of the anemia or not is an open question. Other organic and inorganic compounds are also retained in the blood plasma in renal insufficiency, as for example, indican reported by Monias and Shapiro[24] and inorganic sulphates reported by Wakefield, Power and Keith.[25] The consensus of opinion seems to be that the anemia is the result of a depressed activity of the hemopoietic tissues. Just what substance or substances or, perhaps, toxin may be the ultimate causative factor in the production of anemia remains to be discovered. The close parallelism between azotemia and anemia, however, is very apparent, so much so, in fact, that hemoglobin values around 50 per cent have the same prognostic significance as creatinin values of 5 mg. or more.

Summary. 1. Anemia is almost constantly found in cases of azotemia regardless of the pathologic basis for the renal insufficiency.

2. The anemia is probably due to depressed activity of the hematopoietic tissues.

3. The specific etiologic factor in the production of anemia, if it be a single one, is not known.

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A STUDY OF THE CLASMATOCYTES IN THE SACROSPINALIS MUSCLE OF THE RABBIT.

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The mononuclear phagocytic cells of the animal organism may be arranged in two rather indefinite components of the reticuloendothelial system. Of these the fixed components of the system largely localized in the liver, spleen and bone marrow are often designated reticuloendothelial cells, whereas the migratory or wandering cells, present in every organ of the body, are perhaps best known as clasmatocytes. These wandering phagocytic cells are widely known to the cytologist, and their origin and morphology have been a favorite subject for study, but their functions are not so thoroughly understood by the surgeon and clinician. And yet injury to tissue of one sort or another, abrasions, contusions and surgical wounds, all induce a response by local clasmatocytes which contribute toward the process of recovery. Cellular exudates, either of the pleura or peritoneum, after the third day are practically exclusively clasmatocytic, and their contribution to the formation of fibrous tissues is quite generally recognized.

Although opinions to the contrary maintain, there are experimental data which lead one to conclude that these two systems of cells are not wholly independent of one another. The desquamation and migration of the fixed phagocytes of the liver and their subsequent identification as clasmatocytes is indicative of the opinion that considerable identity between the fixed and the wandering components of the reticuloendothelial system does exist. Such identity was sustained in the work of de Haan and Hoekstra. These authors concluded from perfusion experiments in rabbits that the reticular cell of the liver was identical to the mononuclear cells of a peritoneal exudate. The reaction of connective tissue to foreign irritants has long been a popular field for studies on cellular relationships. Although the literature on the origin, identity and function of these cells is enormous, there is an apparent lack of unity in the interpretation of results. Ekola has given an excellent review of the literature on the clasmatocyte, polyblast and fibroblast, so that any consideration at this time is unnecessary.

Clasmatocytes from various regions of the body, the peritoneum, pleura, omentum, mediastinum and subcutaneous spaces, have been studied with respect to their origin and their function, but we know of no study on the intramuscular reaction to an irritant.

Throughout this study we have considered the possible sources for the origin of these mononuclear phagocytes as well as their function and subsequent transformation.

According to Sabin, Doan and Cunningham the clasmatocyte of animal tissue has a definite cytoplasmic organization which reacts in a characteristic way to supravital stains. It differs from the monocyte, which displays a definite rosette formation in the arrangement of its cytoplasmic granules. Clasmatocytes are remarkably phagocytic and engulf huge quantities of any foreign material. This tendency has rendered them readily visible so that subsequent changes or transformations may be easily followed. By this means Hetherington followed the changes which occurred in the transformations of clasmatocytes and monocytes into epithelioid cells and into giant cells. It is probable that epithelioid cells of pulmonary tubercles arise from the local wandering clasmatocytes which mobilize so rapidly in the presence of any foreign body. The observations of Bloom, in which the transformation of lymphocytes and polyblasts into fibroblasts was seen, is supported by many observations in our laboratory wherein dye-laden mononuclear cells have displayed fibroblastic potencies.

Method. The sacrospinalis muscle of the rabbit, one of the most powerful muscles in the body, was selected as the site for the injections. The hair covering this region was removed and the skin washed and bathed with alcohol. After blocking a portion of the area with procain, 0.5 cc. of a graphite preparation was injected directly into the muscle. The tip of the needle was inserted deep enough to approximate the neural arch of the second lumbar vertebra, and the injection was made as the needle was slowly withdrawn. Ten animals were thus injected and they were killed at intervals ranging from 1 hour to 1 month later. The muscle which had been injected was excised at necropsy, fixed and stained with routine selective stains.

Observations. Inflammation was already manifest in sections of the muscle taken 1 hour after injection. This is in accord with prevailing opinion that decided signs of inflammation may be apparent 30 minutes to 1 hour after the injection of an irritant. Diapedesis had occurred and the graphite mass, together with erythrocytes, neutrophils and monocytes, was enmeshed in a fibrin network. Comparable cells were identified in the adjoining capillaries and there was every indication that the cells of the inflammatory lesion were derived from the blood stream, an observation first described about 70 years ago and since verified by numerous investigators.

At 3 hours after an injection there was tremendous engorgement of capillaries, and neutrophils and monocytes were seen migrating through the endothelium into the interfascicular spaces. Erythro-

cytes, lymphocytes, and monocytes were encountered with the neutrophils within the periphery of the graphite clump, and considerable phagocytosis by the neutrophils had occurred. At 6 hours a few large mononuclear cells, differing from those derived from the blood stream, were encountered in the sections. These were of histogenous origin and we believe were local clasmatocytes or macrophages of the region. Occasional graphite granules were seen in blood monocytes and clasmatocytes, yet phagocytosis at this time was far more active in the neutrophils.

The latter half of the 1st day and the 2d day were marked by an abundant proliferation or increase in the number of clasmatocytes. Capillaries remained congested and the preponderant white cell within these fixed vessels was the monocyte. The neutrophils, so numerous during the first day, were disappearing, degenerating and they were phagocytosed by the mononuclear cells during the 2d and 3d days. Monocytes, bearing graphite granules, were seen in the fixed capillaries, and it was clear that these phagocytic agranulocytes had reëntered the blood stream from the inflamed area. After the second day the mononuclear cells were the only active constituent, and the further resolution and organization of the lesion was purely a function of these nongranular leukocytes of the blood and the macrophages of the tissue.

During the 3d, 4th and 5th days extensive phagocytosis ensued. In fact, all mononuclear cells which now had increased in numbers were heavily phagocytic. Dispersion of the graphite was evidently a function of these cells, for they had a tendency to migrate toward the center of the foreign body, to engulf large quantities of the graphite and then return. With the changes mentioned there was rapid increase and mobilization of fibroblasts. These were spindle-shaped cells with oval nuclei and they were usually nonphagocytic. Fibroblasts are considered only slightly phagocytic and they store engulfed materials rather in the form of fine particles than as large masses, as displayed by clasmatocytes. Contrary to the apparent dispersal function of the clasmatocyte the fibroblasts arranged themselves into a wall which largely circumscribed the lesion, walling off the free graphite and graphite laden cells from the peripheral muscle bundles. Thus heavily laden macrophages were massed along the inner surface of the wall of fibroblasts, unable, except in a few places, to penetrate it. But occasional graphite-laden macrophages appeared within the connective tissue capsule; others had migrated to places remote from the lesion.

It was clear, during the earlier days of the mononuclear reactions that the macrophages of the lesion were of two types. During the earlier stages of inflammation, lymphocytes migrated from the capillaries into the area along with the monocytes. These cells were not at once phagocytic; but if one is to judge by size, staining

reactions of nucleus and cytoplasm, it was apparent that here were transitional stages between lymphocytes and typical macrophages. The basophilic rim of cytoplasm around the oval or spherical nucleus increased in extent, the cell engulfed foreign particles and soon was functionally undifferentiated from the other macrophages of the lesion. Such a transformation of the lymphocyte into a phagocytic cell is wholly in accord with the observations of Bloom and Ekola. In studies of the buffy coat of chicken blood,[9] however, lymphocytes did not transform into clasmatocytes. It is recognized, also, that conclusions drawn from such morphologic evidence alone must be accepted with reserve.

The monocyte, also prevalent in the early reaction, transformed into typical macrophages which became as phagocytic as the tissue clasmatocyte, so that in reactions of 1 week or more it was obviously impossible to detect whether the macrophage was of histogenous or of hematogenous origin. Hetherington has shown that monocytes may increase in size, may lose their typical rosette formation after supravital staining and display a rather patternless distribution of its granules, such as displayed by the clasmatocytes. Thus it appears that these macrophages may have come from three possible sources, namely, the lymphocytes and monocytes of the blood stream and the clasmatocytes of the local connective tissue sheaths of the muscle bundles.

The origin of the fibroblasts which formed the capsule around the foreign body in the muscle is not entirely clear, and yet they are unquestionably of a divergent origin. Fibroblasts are generally considered an end product in that they do not transform into other types of cells, but respond to irritating stimuli by the production of fibrous tissue. There is, however, considerable evidence to the contrary. Von Möllendorff is of the opinion that fibroblasts possess widely divergent possibilities and that they may transform into blood or other tissue cells. Lindsay and Ekola consider the fibroblast a potential clasmatocyte. There is no evidence from our study to indicate that preëxisting fibroblasts may transform into clasmatocytes, although such a relationship is not denied. It appears quite certain, however, that these fibroblasts which produced the fibrous capsule are derived from three sources. Some of them were present in the muscle, and at the time of injection were mobilized around the lesion. Others arose from transformed lymphocytes which were derived from the capillaries, while a third group were transformed clasmatocytes. Furthermore, many of these clasmatocytes, after engulfing quantities of graphite, became a part of the peripheral fibrous capsule and produced characteristic fibrous tissue. Such a transformation of clasmatocytes and polyblasts into fibroblasts has been frequently described.

Comment. Throughout this study the probable origin of the phagocytic cell which characterized the reaction to graphite injected intramuscularly was kept constantly in mind. The endothelial origin of clasmatocytes was first suggested by Mallory and later developed by McJunkin, Foot, Herzog, and Sabin and Doan. Contrary opinions have been expressed by Lang and Clark and Clark. In sections taken from these 10 animals, during the 28 days of observation, we found no evidence to indicate an endothelial origin for the large number of clasmatocytes encountered. Even during the 2d and 3d day, when congestion was marked and diapedesis common, we have never seen an endothelial cell desquamate and migrate through the wall to the lesion.

In another experiment to test the phagocytic activity of the endothelium, we perfused isolated hearts with heparinized whole blood to which a small amount of graphite had been added. After perfusing a heart for 4 to 6 hours, sections of the myocardium, including endothelium, were removed, fixed, stained and examined. Under such conditions graphite granules were never encountered within endothelial cells. True, granules were adherent to the cell membranes, but not actually within the cytoplasm. Smears of the circulating blood, however, showed that the monocytes had engulfed considerable graphite, and they were not unlike those seen in the sections of the intramuscular lesion. The experiment gave no evidence that endothelium was phagocytic, nor that it contributed toward the formation of clasmatocytes.

Definite evidence that clasmatocytes were derived from blood monocytes was presented by Lewis and Lewis. Such changes, however, had been previously suggested by other workers. Our data lead us to conclude that the lymphocytes as well as the monocytes which entered the field of inflammation from the related capillaries transformed into clasmatocytes. Although lymphocytes are not normally phagocytic, yet in the presence of continuous irritation we observed what appeared to be steps in a gradual transition to small but functional clasmatocytes. Likewise the monocytes which normally have a restricted phagocytic tendency and a characteristic granular arrangement, gradually assumed clasmatocytic characters. Thus, after the 4th or 5th day lymphocytic or monocytic clasmatocytes could not be identified from those which were of histogenous origin.

At the conclusion of the period of observation a well defined connective tissue capsule had been formed around the graphite lesion, walling it off from functional muscle. The fibroblasts comprising or forming this wall we believe were of three sources: lymphocytes, local fibroblasts and clasmatocytes. Only a portion of the clasmatocytes apparently transformed into fibroblasts and whether they were of lymphocytic, monocytic or of histogenous origin we do

not know. Clasmatocytes well laden with dye seemed to become a part of the fibroblastic wall, and apparently gave rise to fibrils, for engulfed graphite particles were detected in the attenuated cytoplasmic bodies.

The ultimate fate of most of the clasmatocytes appeared to be degeneration. Those that did not transform into fibroblasts were cut off from the circulation, and autolysis quickly ensued.

Conclusions. Clasmatocytes which were produced on the 2d and 3d day in response to a graphite injection into the sacrospinalis muscle of the rabbit apparently arose from three sources: lymphocytes and monocytes of the blood stream and local wandering cells of the tissue spaces. After the third day these clasmatocytes could not be distinguished from one another.

The function of the clasmatocyte was to engulf the foreign material, to disperse and lessen its concentration, to convey portions of it to the blood stream and thence to the reticuloendothelial system.

After the 3d day a fibroblast wall was laid down around the graphite area. This wall restricted the further dispersal activity of the clasmatocytes and localized the foreign body. Fibroblasts also appeared to arise from three sources: lymphocytes, clasmatocytes and local fibroblasts. The number of clasmatocytes, with heavily laden phagocytic materials, which transformed into fibroblasts was small. The larger number, within the circumscribing wall, degenerated.

There was no evidence that endothelium gave rise to clasmatocytes.

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STUDIES IN RHEUMATIC FEVER.

I. THE NATURAL COURSE OF ACUTE MANIFESTATIONS OF RHEUMATIC FEVER UNINFLUENCED BY "SPECIFIC" THERAPY.

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THE unitary nature of the manifestations of rheumatic fever was first implied when Pitcairn[1] recognized the relationship of pericarditis and rheumatic polyarthritis. Cheadle[2] linked the various manifestations which he called the rheumatic series and used the term the rheumatic state to denote the general nature of the disease. Barlow and Warner,[3] who described the subcutaneous nodule, suggested the similarity between the changes seen in this lesion and the valvular lesions.

The anatomic basis for the concept of the unitary nature of rheumatic fever was laid with the description[4,5] of the submiliary myocardial nodule. Studies of the pathologic changes in blood-vessels and supporting tissues[6,7,8,9] have identified widespread lesions as part of the rheumatic state.

Disturbances in cardiac rate and rhythm[10] and alterations[11] in the electrocardiograms have been shown to occur in a large number of patients with acute rheumatic polyarthritis. Previously acute heart block had been correlated with inflammatory changes in the *A–V* bundle found at necropsy.[12,13]

Bacteriologic reports (Poynton and Paine,[14] Small,[15] Birkhaug[16] and Swift[17]), claiming a specific or related rôle for organisms found, led to the introduction of antisera and vaccines for the treatment of patients with active rheumatic fever. With the increasing interest in etiologic factors and a better understanding of the nature of the disease the paucity of properly controlled therapeutic studies is surprising.

Latham[18] recognized the need for clinical control studies. In 1845 he wrote: "Acute rheumatism has experienced strange things at the hands of medical men. No disease has been treated by such various and opposite methods. Venesection has wrought its cure, and so has opium, and so has calomel, and so has colchicum, and so have drastic purgatives. I speak of these remedies in the sense which medical men imply when they talk (as they sometimes do) of this, that, or the other thing being their 'sheet anchor;' meaning that they rest upon it alone for the cure of the rheumatism, and employ other remedies either not at all, or for very subordinate purposes. And, indeed, I bear my testimony to the success of each of these different remedies, so far as that, under the use of each, I have seen patients *get* well."

Gull[19] and Sutton[20] studied a series of patients with mint water and observed subsidence of the disease. Hall[21] (1876), Fagge[22] (1881), Reihlen[23] (1886) studied patients treated with salicylates and compared them with cases not receiving the drug. Hanzlik, Scott and Gauchat,[24] observing effects on temperature, pulse and symptoms in salicylate treated cases, concluded that the drug possessed no specificity in rheumatic fever.

While there is no question of the therapeutic benefit of antirheumatic drugs, many have undoubtedly felt, as Poynton[25] has recently commented, that the rheumatic infection often proceeds unchecked in spite of defervescence and the increased comfort of the patient. He concludes that there are few physicians today who regard salicylates as specific in the treatment of rheumatic fever. Furthermore, Swift[26] has stated: "Most statistics indicate that the administration of salicylates does not decrease the incidence of carditis and clinical evidence of this manifestation often appears in patients fully under the influence of antirheumatic drugs." He refers to the figures of Ehrström and Wahlberg,[27] in Helsingfors, which indicate that there has been no diminution in the incidence of chronic rheumatic heart disease.

We felt that the study of a control group of patients might be undertaken if we carefully guarded our patients from excessive discomfort by the use of sedatives or hypnotics, whenever necessary. We decided further that we would not jeopardize a single patient by withholding antirheumatic drugs if he appeared extremely ill or in critical danger. To this end we resolved to give antirheumatic drugs to all patients developing rectal temperatures exceeding 105° F. (It was not necessary to do this in a single instance.) All other therapeutic measures, dietary and nursing care, immobilization of joints, applications of cradles, were to be applied with special attention.

We also felt that such a study might be undertaken because of previous experience. The very low mortality from acute rheumatic fever has been realized for a century and prior to the introduction

of the antirheumatic drugs. In our experience when antirheumatic drugs were withheld from patients, for one reason or another, fatalities were most unusual.

Method of Study. Upon admission of the patient the house officer notified one of us, a special detailed history was taken, and the findings of the physical examination were recorded upon a special form. Care was used in determining the exact date of the onset of the disease, and in investigating the patient's antecedent history. Members of the patient's family and his physician were interviewed, and when necessary a home visit was made to amplify such data by a special medical social worker.

Pulse rate and rectal temperature were taken every 4 hours. A complete blood count was done on admission and at least twice a week during the acute stage and once a week until the patient was discharged. An electrocardiogram was taken on admission, and at least twice a week during the acute stage and once a week until the patient was discharged. In cases developing acute pericarditis, or gallop rhythm, or showing first-stage A–V block, or any irregularity, electrocardiograms were taken daily or twice daily as indicated. With the subsidence of acute symptoms, tracings were made weekly. Blood cultures were done on all patients at frequent intervals. Skin tests, using streptococcus filtrates, were made at frequent intervals on the patients seen during the 2 years of the study. The results of the bacteriologic studies, skin tests and detailed electrocardiographic studies will be reported elsewhere. As soon as possible after admission a teleoroentgenographic study of the heart was made. Roentgenograms were made of the teeth, nose, throat and accessory sinuses. The urine was examined on admission and frequently thereafter. In addition to being seen by the house officer, patients in the series were seen daily and twice or more daily during the acute stage by us, and notes made on their clinical records. A graphic chart devised by Swift was kept on all cases so that daily correlations could be made. Full-time fellows, special nurses and special medical social service workers were used in addition to the regular hospital staff.*

Treatment. Patients were placed on Gatch beds, painful joints were protected with cotton wool, and if desired camphorated oil was applied. Pressure from bedclothes was relieved by a cradle. Pain was controlled by codein and only once in the course of the study was morphin required. When infected foci were found every effort was made to eradicate them. A special diet was given these patients, and extra efforts were made to force fluids.

During the 2 years 162 patients suffering from acute rheumatic fever were studied. Of this number 50 were treated with salicylates or with vaccine. In this report we are discussing the observations

* From the Rheumatic Fever Fund of the Committee for the Encouragement of Medical Research.

made on 105 patients receiving no form of therapy, which might be believed to be specific, and no antipyretic drug. The patients were divided into three groups: (*a*) In the first we placed patients with polyarthritis, with acute active manifestations, who had no previous history of rheumatic disease and no heart involvement, and patients who had previously had signs of heart involvement which had been clinically inactive for a long period of time and who showed little or no diminution of cardiac reserve; (*b*) the second group consisted of patients whose chief manifestation was chorea; (*c*) the third group consisted of patients with a history of repeated rheumatic infections and advanced structural heart disease. As we were concerned with the natural course of active manifestations of rheumatic fever, we accepted no patients with inactive forms of the disease in this series.

The following criteria* were used to determine the cessation of the active phases of the infection: (1) The rectal temperature was to remain consistently below 99.6° F.; (2) the pulse rate was to remain consistently below 100 per minute; (3) the total leukocyte count was to be below 10,000; (4) absence of cardiac signs such as gallop rhythm, prolonged *P–R* interval, or other significant electrocardiographic changes, and pericardial friction rub; (5) no evidence of pulmonic or pleural infection; (6) no choreiform movements, subcutaneous nodules or skin manifestations of rheumatic fever.† When patients showed no deviation from these standards for a full 2-week period following the last sign of activity, they were considered ready for discharge.‡

Only 47 of the 105 patients remained in the hospital until these criteria had been fulfilled. Fifty-seven patients left for various reasons; 40 because their symptoms had cleared up and they could not be persuaded to remain for the full 2-week period and 17 left despite evidence of activity and against the advice of the physician in charge. All of these patients were much improved.

Forty-seven patients fulfilled all the requirements of this study (35 males, 12 females; see Table 1): These were divided into the 3 groups previously described; 29 in the polyarthritis group, 6 in the chorea group and 12 in the carditis group.

In 15 of the 29 patients in the polyarthritis group sore throat or tonsillitis occurred at the onset of the disease or during the course of the disease. In 2 of the patients with chorea tonsillitis occurred

* The possibility that the criteria in general use as well as those we have used are not adequate must be kept in mind. (Witness the occasional patient presenting unmistakable signs of rheumatic heart disease with an entirely negative history.)

† We are cognizant of the desirability of determining the sedimentation rate of erythrocytes as a sign of continued infection. The study herewith submitted was almost completed when our attention was drawn to the desirability of this procedure.

‡ Only 1 patient of the entire group suffered a second cycle within a month of discharge.

during their hospital stay. Tonsillitis occurred in only 1 of the patients classified as chronic active carditis.

TABLE 1.—MANIFESTATIONS OF RHEUMATIC FEVER.

Patient.	Age.	Sex.	No. of present attack.	Duration of disease (onset to discharge).	Duration of signs or symptoms.	Days in hospital.	Fever.	Tachycardia.	Sore throat or tonsillitis.	Polyarthritis.	Pericarditis.	A-V block.	Gallop rhythm.	Heart failure.	Pleurisy.	Pneumonitis.	Skin manifestations.	Subcutaneous nodules.	Chorea.	Died.
Polyarthritis.																				
1. W. S.	15	M	1	23	7	22	+	+	..	+										
2. J. K.	39	M	4	25	11	22	+	+	..	+										
3. L. R.	12	F	3	26	11	24	+	+	+	+	..	+	..	..	..	..	..	+		
4. H. G.	18	M	1	37	20	26	+	+	..	+										
5. S. K.	31	M	2	58	30	46	+	+	..	+	..	..	..	..	+					
6. E. W.	18	M	2	49	32	43	+	+	+	+										
7. M. W.	23	M	1	65	42	56	+	+	+	+										
8. M. D.	47	M	3	60	45	58	+			+	..	+								
9. F. N.	46	M	2	60	46	57	+	+	..	+										
10. E. B.	44	M	4	69	49	46	+		+	+	..	+								
11. C. V.	24	M	1	81	50	55	+	+	..	+	..	+								
12. A. Li.	33	M	1	93	54	88	+	+	+	+										
13. A. Le.	13	F	2	73	56	60	+	+	..	+	..	+	+							
14. J. D.	36	M	2	71	57	50	+		+	+										
15. H. K.	21	M	1	80	57	75	+	+	+	+	+	+	..	+						
16. W. M.	30	M	4	83	60	83	+		..	+										
17. L. L.	38	M	4	75	61	70	+	+	..	+										
18. S. Ma.	22	M	1	92	70	71	+	+	..	+										
19. D. I.	27	M	2	90	72	52	+	+	..	+										
20. S. Mi.	35	M	1	95	72	79	+	+	+	+				+						
21. M. P.	15	F	2	88	73	85	+	+	..	+	+	..	..	+						
22. O. McG.	38	M	4	95	73	92	+	+	+	+	..	+	+	+	..	..	+			
23. A. S.	45	M	2	88	74	79	+	+	+	+	+	+	..	+						
24. H. S.	31	M	1	95	77	79	+	+	+	+	+	..	..	+	+	+				
25. G. deM.	17	M	1	98	78	78	+	+	+	+										
26. G. H.	31	M	2	108	82	105	+	+	..	+	+	..	+	+	+					
27. H. M.	24	M	2	101	87	95	+	+	+	+	..	+	+	+						
28. W. I.	25	M	1	113	87 not less	92	+	+	+	+	..	..	..	+						
29. C. O.	24	M	3	..	25	53	+	+	..	+										
Chorea.																				
30. B. D.	14	F	1	70	56	40	+	+	..	..	..	..	..	..	..	..	..	..	+	
31. H. W.	13	M	1	71	56	55	+	+	..	..	..	..	..	..	..	..	..	..	+	
32. J. M.	15	M	1	112	87	105	+	+	..	..	..	..	..	..	..	..	..	..	+	
33. A. P.	12	F	2	112	92	58	+	+	+	..	..	..	..	..	..	..	..	..	+	
34. R. B.	12	M	1	176	113	148	+	+	..	..	..	..	..	..	..	..	..	..	+	
35. A. C.	12	F	1	167	152	77	+	+	+	..	..	..	..	..	..	..	..	..	+	
Active chronic carditis.																				
36. E. G.	14	F	4	..	..	15	+	+	..	..	+	+	..	+	+	..	..	..	..	+
37. C. B.	33	F	5	..	..	20	+	+	..	..	..	..	..	+	..	..	+	..	..	+
38. E. C.	13	M	1	..	..	34	+	..	..	..	..	..	..	+	..	..	+	..	..	
39. J. S.	13	M	5	..	..	36	+	+	..	..	..	+	..	+						
40. E. P.	29	M	2	..	..	36	+	+	..	..	..	..	..	+	+	+	..	..	..	+
41. P. H.	30	F	3	..	..	38	+	+	..	..	..	..	..	+						
42. M. P.	25	F	?	..	..	84	+	+	..	+	..	..	..	+	..	..	+	..	..	+
43. J. U.	18	M	3	..	..	94	+	+	..	..	..	+	..	+	+	..	..	..	..	+
44. I. H.	15	F	?	..	..	129	+	+	..	..	..	+	..	+	+	+	+	..	..	+
45. S. I.	34	M	4	..	..	140	+	+	..	..	..	..	..	+	..	..	+			
46. W. O'B.	31	M	5	..	..	148	+	+	..	..	..	..	..	+						
47. M. D.	25	F	1	..	..	169	+	+	+	..	..	..	..	+						

TABLE 2.—AGE DISTRIBUTION.

Under 20 years	18
20 to 29 "	11
30 to 39 "	14
40 to 49 "	4

Pericarditis occurred in 5 patients in the polyarthritis group and in 1 patient in the chronic active cardiac group. Murmurs alone were considered too indefinite a sign of activity to be used as evidence of carditis.

Gallop rhythm occurred in 4 patients of the polyarthritis group. Signs of congestive heart failure appeared in 9 of the polyarthritis group and in all of the chronic active carditis group.

Pleurisy developed in 2 patients in the polyarthritis group and in 4 patients in the chronic active carditis group.

Pneumonitis of a type not characteristic of lobar pneumonia was seen in 3 patients, 1 in the polyarthritis and 2 in the chronic active carditis group. These were believed to be rheumatic pulmonary manifestations.

Skin manifestations occurred in 6 patients, 1 of these was in the polyarthritis group and 5 of the chronic active carditis group, and 1 patient in the polyarthritis group developed subcutaneous nodules. In considering the manifestations in relation to the possible effects of therapeutic procedures, it is to be emphasized that there is great variability as to the type and number.

TABLE 3.—FREQUENCY OF MULTIPLE MANIFESTATIONS IN RELATION TO THE DURATION OF SIGNS OF ACTIVE RHEUMATIC FEVER.

	Duration of signs or symptoms.		
	46 days or less.	47 to 70 days.	70 to 87 days.
Number of cases	9	9	10
Fever	9	9	10
Tachycardia	8	6	10
Sore throat	3	4	8
Polyarthritis	9	9	10
Pericarditis	0	1	4
A–V block	2	4	3
Gallop rhythm	0	1	3
Heart failure	0	1	8
Pleurisy	1	0	2
Pneumonitis	0	0	1
Skin manifestations	0	0	1
Subcutaneous nodules	1	0	0
Chorea	0	0	0

A relation was noted between the duration of active signs or symptoms and the number of manifestations. With activity for less than 46 days (9 patients), fever, tachycardia and polyarthritis were accompanied by tonsillitis (or sore throat) in 3 cases, by *A–V* block once, by pleuritis once and 1 appearance of subcutaneous nodules (Table 3). With activity from 46 to 70 days (9 patients), fever, tachycardia and polyarthritis were accompanied by tonsillitis (or sore throat) in 4 cases, by pericarditis once, *A–V* block 4 times, gallop rhythm once (during *A–V* block), signs of heart failure once. With signs of disease for more than 70 days (and in our observations up to 87 days), the frequency of multiple manifestations is seen to be sharply increased. In this group all 10

patients had fever, tachycardia and polyarthritis. Tonsillitis (or sore throat) occurred 8 times, pericarditis 4 times, *A–V* block 3 times, gallop rhythm 3 times (twice in association with *A–V* block). Signs of heart failure appeared in 8 patients, pleurisy occurred in 2, pneumonitis in 1 and a skin manifestation in 1.

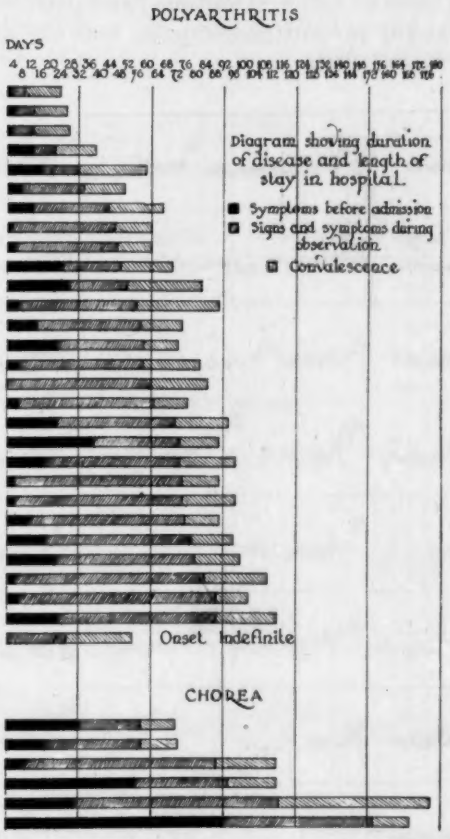

CHART I.—A diagram showing the duration of disease and the length of stay in the hospital of 29 patients with polyarthritis and 6 patients with chorea.

Swift[28] reported 72 cases "treated according to the accepted methods, with rheumatic drugs for arthritis and high fever, removal of such disease foci as tonsils or teeth and treatment of diseased sinuses or other suspected foci." He used criteria identical with those used by us in considering patients ready for discharge. If we exclude 24 of his cases which were below the age of 14 years we have a group of 48, comparable to this series both in number and age grouping. In his total group the illness varied between 30 and 220 days. Although the two groups are not absolutely comparable,

we think it is evident that the elimination of antirheumatic drugs, at least, did not prolong the duration of the disease (Chart I).

Patients with a history of previous rheumatic infections, showing badly damaged hearts, and who had as a presenting symptom signs of subacute cardiac activity, had the longest period of illness. In this group the only deaths occurred. Patients with chorea had the next longest period of active symptoms, and patients admitted with polyarthritis as the presenting symptom had the shortest duration of the disease.

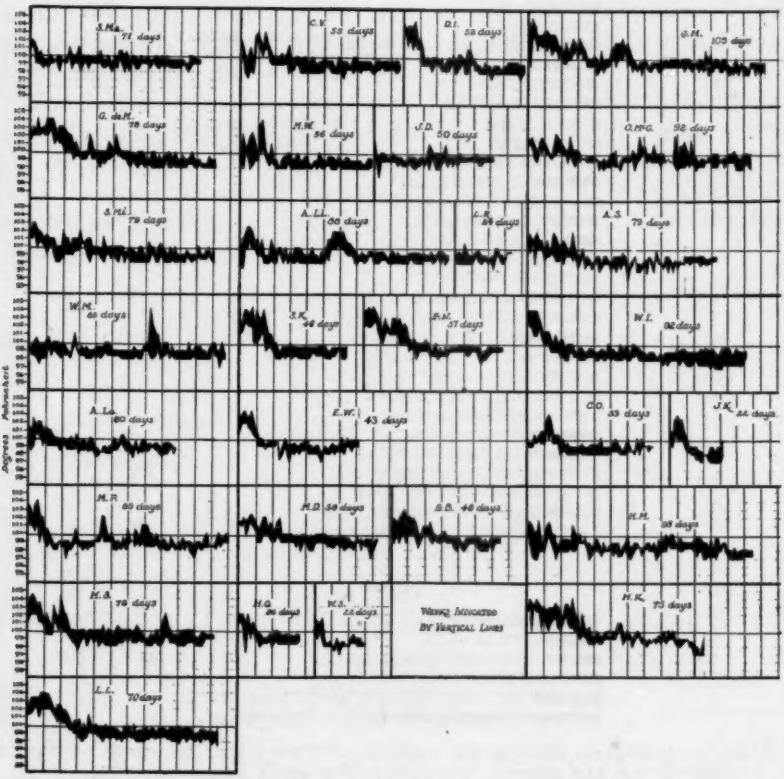

CHART II.—Temperature variations in 29 patients with rheumatic fever and polyarthritis.

Duration of Illness. The illness was considered to have begun upon the first definite history of rheumatic manifestation and to continue until the patient was free from any evidence of activity for 2 weeks. In the group of patients with chronic carditis the onset was more indefinite than in the other 2 groups. We believe that the period of activity often extends for years.

No relationship was found between the length of the attack,

length of illness, sex, age and number of attacks. It was also found that there was no appreciable difference in the duration of the attack when this was correlated with the time of the entrance to the hospital, whether early or late in the disease. The longest period of activity was observed in patients with chorea or chronic active carditis.

In the polyarthritis group activity was increased in patients who developed pericarditis or signs of heart failure and slightly increased for those who developed a P–R interval of the electrocardiogram

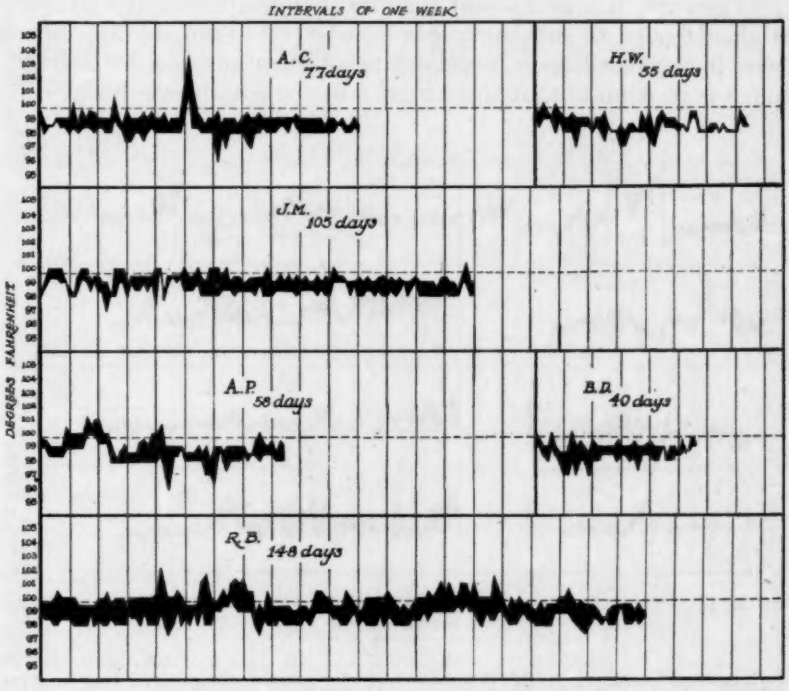

CHART III.—Temperature variations in 6 patients with rheumatic fever and chorea.

of over 0.2 second. However, none of the patients with pericarditis or prolonged interval had such manifestations alone. When either of these manifestations occurred the activity lasted for 6 weeks or more. There were 2 exceptions, 1 patient in the polyarthritis group and 1 patient in the chronic active carditis group who had a rapidly fatal course.

Tonsillitis, at the onset or during the disease, was present in 9 of the patients (Nos. 20 to 28, inclusive) in the polyarthritis group whose illness was longest and characterized by multiple manifestations and considered the most severely ill.

Temperature. In the polyarthritis group 10 patients had a single bout of fever, 6 patients had 2 cycles, 3 patients had 3 and 1 patient had 4 cycles of fever. The shortest duration of any cycle of fever was 5 days, the longest 56 days. The highest temperature in our group was 105° F. Thirteen of the patients had temperatures which ranged up to 104° F. As a rule, in the polycyclic forms the second cycle was not as high and the duration of fever was not as long, but this did not always hold true. As might be expected, the duration of the fever was usually associated with new manifestations or recurrences of old manifestations of rheumatic fever (Chart II).

In general, it may be said that the temperature of the patients studied tended to subside spontaneously. It is possible to control fever in rheumatic fever by salicylates or other antirheumatic drugs, but it is recognized that such drugs must be withdrawn during con-

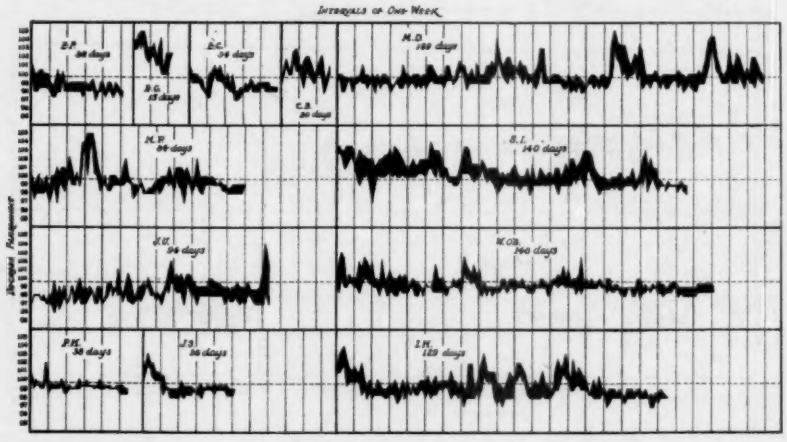

CHART IV.—Temperature variations in 12 patients with rheumatic fever and chronic active carditis.

valescence in order to determine that the active process of the disease has ceased, and that unless patients are subjected to a period of observation, free from the administration of antirheumatic drugs, many patients will be discharged while the disease is still active.

Our experience shows us that the temperature of rheumatic fever patients becomes and remains normal without the use of antirheumatic drugs. Further, more than half of the patients had only a single cycle of fever. It is important to emphasize these spontaneous remissions in considering any mode of treatment. In the chorea group all of the patients did not have fever, but those who did ran a low-grade and persistent elevation of temperature. Fever in the patients in the chronic active carditis group, as a rule, persisted longer and was irregular, though in some it may have been said to be polycyclic (Charts III and IV).

Joint Involvement. Considering all joint symptoms together without reference to intensity, 2 cases were found to have a maximum of 16 joints involved, 1 case had only 2 joints involved, while 16 of the 30 showed involvement of 6 to 12 joints.

With reference to the intensity of joint involvement, we find that 24 cases had severe arthritis, 1 of these had 12 joints acutely inflamed and extremely painful at one time; but of the 24 cases 12 had 6 joints or less involved; 2 cases had only 1 joint severely inflamed (Chart V).

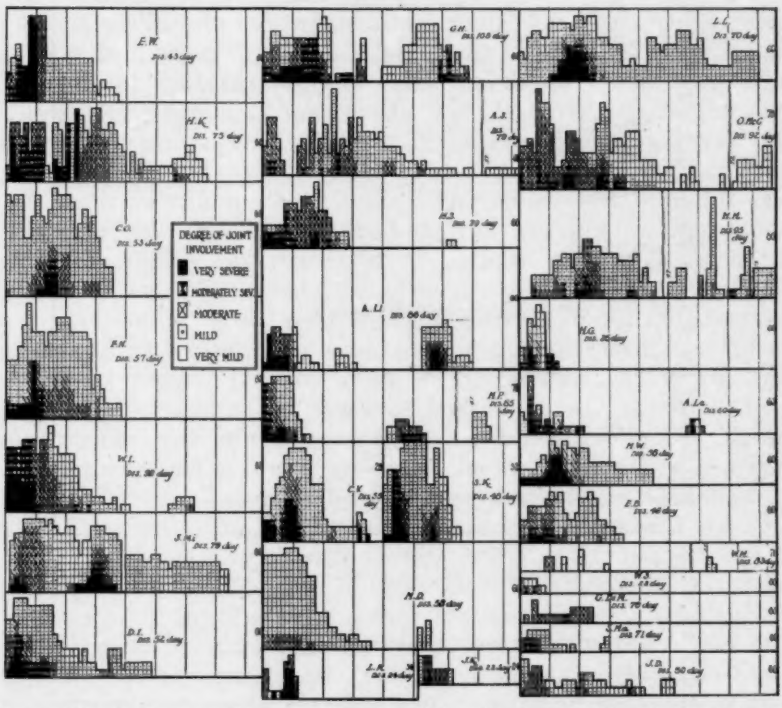

CHART V.—A chart to show the degree and duration of joint involvement in 29 patients with rheumatic fever and polyarthritis.

Recurring attacks were always milder than the initial attack. In only 1 of the recurrences was polyarthritis observed which could be rated as severe.

Untreated arthritis usually subsided in a week (22 out of 29). In over half of the patients there was no recurrence of arthritis, and when there were recurrences they uniformly affected fewer joints and were less severe and of shorter duration than the initial attack. Cases were encountered which showed spontaneous subsidence of arthritis as abrupt and complete as those seen in cases in which salicylate therapy has been instituted.

Heart Block. Of 29 cases of polyarthritis 9 developed *A–V* block, using the *P–R* interval of 0.2 second as a criterion for the presence of block. It is realized that this is a strict interpretation of auriculoventricular block, but all of these patients satisfied the criterion laid down by Cohn and Swift, that there be an increase of 0.06 second above the normal. Of 12 cases of chronic carditis 4 devel-

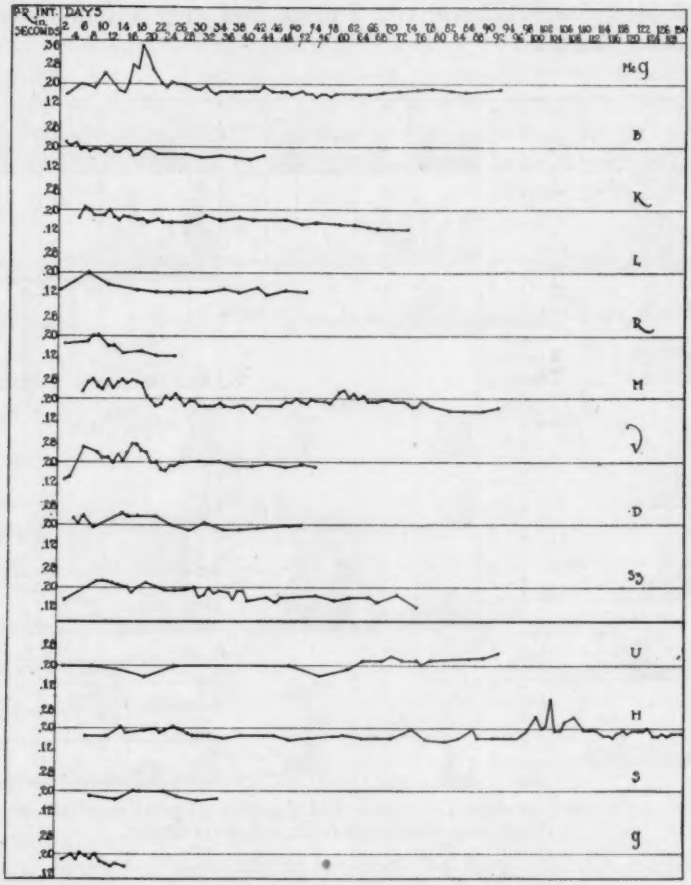

CHART VI.—A chart to show variation in the *A–V* conduction time during the course of rheumatic fever uninfluenced by salicylate therapy. Time in days is plotted along the abscissa; the *P–R* interval in seconds is plotted along the ordinate. The first 9 curves are from patients with rheumatic fever and polyarthritis; the last 4 curves are from patients with rheumatic fever and chronic active carditis.

oped *A–V* block. It would seem from these cases in both groups, as well as from a much wider experience with patients receiving salicylates, that *A–V* block, occurring in the course of acute cardiac manifestations of rheumatic fever, is subject to wide variations and is usually of short duration. Its occurrence may be monocyclic or polycyclic, and its persistence may be variable (Chart VI).

The maximum *P–R* interval in this group of cases was 0.36 second. It usually ranged between 0.2 and 0.26 second. The variations in block as to degree, persistence and recurrence are important when one attempts to determine criteria for judging the effect of a therapeutic agent on *A–V* block. The consideration of the presented facts showed that in the course of acute rheumatic fever unmodified by therapy there are wide and inconstant variations of the *P–R* interval. Elsewhere a study[29] has been reported from this clinic in which it has been shown that variations of the *P–R* interval are not influenced by salicylate therapy.

Tachycardia. In the polyarthritis group 15 patients had a single cycle of tachycardia. Five had 2 and 4 had 3 cycles of tachycardia. In 4 patients no tachycardia was observed during the hospital stay. The shortest period of tachycardia was 24 hours and the longest continuous period was 52 days. The highest rate noted was 140 and occurred in 1 patient. The maximum rate in 8 patients was 130 beats per minute; in 10 it was 120; in 5 it was 110; in 2 it was 100; in 3, 95. Tachycardia as a sign of activity occurred alone sometime during observation in 8 patients of the polyarthritis group. Frequent isolated days of tachycardia were noted but, as a rule, elevations of the pulse rate above 100 beats per minute were associated with other manifestations. We encountered 4 instances where the pulse rate never exceeded 95, and ranged between 85 and 95 in spite of the presence of fever, inflamed joints, or *A–V* block. In 5 patients tachycardia, persisting after the subsidence of all other manifestations, prolonged the illness from 1 to 18 days.

In the chorea group tachycardia was present on admission in only 1 patient. The maximum rate was 130, noted in 1 patient; 4 exhibited a maximum rate of 110, and the 6th patient had a maximum rate of 120. One of the 6 patients exhibited tachycardia with no other manifestation during the hospital stay for a period of 2 weeks. In the other instances tachycardia was associated with other active manifestations and occurred as an isolated observation rarely in 2 cases. In this group sustained tachycardia was unusual. Where it did occur it was associated with other intercurrent manifestations, that is, tonsillitis or sore throat.

In the group of chronic active carditis tachycardia accompanied fever in 5 patients. It lasted less than 1 week in 1 case and occurred alone in 4 cases. It was altogether absent in 1 instance.

In general, it may be said that tachycardia like fever tended to subside spontaneously. Tachycardia in the absence of fever or any other manifestation is not an unusual sign in the natural course of active manifestations of rheumatic fever.

Fatalities. Deaths occurred only in the chronic active carditis group. There were 6 deaths in patients who were admitted with advanced structural heart disease and signs of active rheumatic fever. Progressive heart failure consequent and in association with active infection accounted for 5 of these deaths. The sixth was in

a young girl who ran a rapidly downhill course characterized by fever, pericarditis, *A–V* block, profound toxemia and moderate congestive failure.

Summary. In adolescence and adult life the acute manifestations of rheumatic fever tend to subside spontaneously. These manifestations vary in number, degree and duration.

If changes in the number, degree and duration of manifestations are used as criteria for determining the effect of therapeutic agents such changes must be compared either with a standard control group of rheumatic fever patients of known age, sex, racial and proper geographic distribution, of sufficient size to meet statistical requirements; or controlled cases must be studied simultaneously with cases receiving "specific" therapy, in sufficient number so that it may be determined whether or not the effects associated with treatment are not simply variations attendant on the natural course of the disease.

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FUNCTIONAL BUNDLE-BRANCH BLOCK (PARTIAL) PARADOXICALLY RELIEVED BY VAGAL STIMULATION.

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Although bundle-branch block is in the vast majority of cases caused by anatomic changes affecting one of the bundle branches, it was demonstrated by Cohn and Lewis[1] and other observers that it may occur without any demonstrable lesion. To explain such phenomena, we must assume the presence of certain functional disturbances interfering with the free passage of the impulse along one of the branches.

The possible factors that may cause such disturbances during life without leaving any permanent damage discoverable on post-mortem examination are bundle-branch fatigue, toxic states, local interference with the blood supply, and nervous inhibition. In all these cases, variability in the grade and form of block from time to time, corresponding with the variations in the degree of the causative factor or factors, is to be expected.

There are no clear-cut clinical examples found in the literature of bundle-branch block caused by toxic states. Experimental evidence of such conditions, however, is found in the work of Lewis and Mathison.[2] Likewise, no clinical example of such block as being caused by local diminution of the blood supply to one bundle branch has been recorded. Oppenheimer and Williams[3] report a case of complete heart block with frequent shifting and changing electrocardiographic complexes during life, and the only post-mortem lesion was sclerosis of the nodal artery. We may, therefore, infer from this case that a similar condition may also account for occasional bundle-branch block.

Although toxic states and local interference with the blood supply as causes of bundle-branch block have not fully been established, fatigue of the conducting apparatus in the ventricles as well as vagal inhibition causing such block are fairly well proved. It is true that the clinical reports even of such instances are not many.

Noteworthy examples of fatigue as the cause of such block and other aberrations of ventricular complexes are those of Samet,[4] Stenström[5] and Willius and Keith.[6] Samet's case was a male, aged 50 years, presenting evidence of arteriosclerotic heart disease with periods of 2 to 1 heart block. The Q–R–S conduction time was normal during the period of block, but greatly prolonged when the ventricles responded to every auricular impulse. In other words, prolonged rest of the bundle branches caused by auriculoventricular block

restored them to normal functional ability. Stenström presents 2 cases of bundle-branch block. In each, the block was abolished by slowing the heart. Willius and Keith present 3 cases with aberrant *Q–R–S* complexes during decompensation, which returned to normal when compensation was restored. They attribute such aberrances

FIG. 1.—Right (new terminology, left) bundle-branch block. Rate about 84, rhythm regular. The *P–R* interval is very short, the maximum being 0.10 second. There is a definite variation in the lengths of the *P–R* interval even in the same lead the shortest being 0.04 second. The *Q–R–S* conduction time is 0.12 to 0.14 second.

to fatigue of the interventricular conducting apparatus during decompensation.

The more common cause of functional bundle-branch block is nervous inhibition, the vagus being the effective nerve.

That the vagus influences the interventricular as well as the supraventricular portions of the conducting apparatus was demonstrated

by Ritchie,[7] Cohn,[8] and Einthoven and Wernuge.[9] Wilson was able to produce bundle-branch block by vagal stimulation in a very interesting case that he reported.[10] In a recent paper by Wolff, White, and Parkinson,[11] 11 cases of bundle-branch block occurring in young and otherwise healthy people are described. In each case, the block was abolished by exercise or atropin which removed vagal effect, demonstrating the dependence of such block on the vagus. We have recently seen a similar case in the cardiac clinic of the New York Post Graduate Hospital. A 16-year-old boy came for examination because he was told that he had heart disease. He had

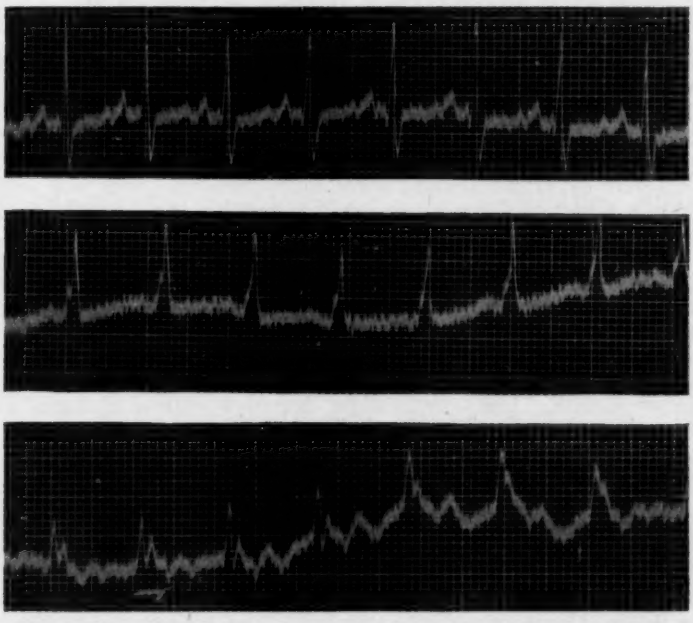

FIG. 2.—Tracings obtained from the same patient as in Fig. 1 after 30 hops on one leg. Rate 150; regular sinus rhythm. *P–R* conduction about 0.16 second. *Q–R–S* conduction 0.08 second.

no complaints, and the physical examination revealed nothing abnormal except a faint transient systolic murmur. The electrocardiogram (Fig. 1), however, showed bundle-branch block with a short *P–R* interval as described by the above authors. After exercising the patient, the ventricular complexes assumed a more normal appearance. The *Q–R–S* conduction time became normal and *P–R* interval was prolonged (Fig. 2).

All these instances prove conclusively the possibility of the occurrence of bundle-branch block as a result of excessive vagal activity in certain cases. It would therefore appear irrational and paradoxical to expect the removal of such block by vagal stimulation.

The following case showing such a condition is therefore considered interesting enough to be put on record.

Case Report. C. E., male, aged 41 years, real estate operator, married, complained of pain in the precordium. The pain appeared spontaneously about once in 3 days, each attack lasting only about 2 or 3 seconds, and was described as sudden, sharp, and knifelike in character. Between these attacks, the patient felt quite comfortable, never experiencing any dyspnea, palpitation, precordial oppression, or any other symptoms attributable to heart disease. He was able to carry on his work well, doing at times a great deal of climbing hills without the slightest discomfort.

His father died at 44 years of age as a result of an accident, and his mother died at 52 of pneumonia. One brother was living and well.

His personal habits were good except for indulgence in alcohol and tobacco. He was married 7 years and had had 1 child who is living and well.

His past morbid history consisted of measles and whooping cough in childhood, appendectomy at 20 years, and gonorrhea at 22 years with no sequelæ.

The physical examination revealed a well-developed, healthy-looking male, calm in demeanor. Pupils reacted normally. No exophthalmos, no nasal or evident accessory sinus pathology. Teeth and gums were normal. Tonsils were hypertrophied and chronically diseased. Neck was negative. Chest was of normal shape, no asymmetry, bulging or abnormal pulsations. Lungs were negative.

The heart and aorta were of normal size and shape, as evidenced by physical and fluoroscopic examinations. The maximum apex impulse was in the fifth interspace, about 9 cm. from the midsternal line, and percussion dullness extended about ½ cm. further to the left in the same interspace. The right border in fourth space was about 4 cm. from the midsternal line. The transverse arch measured about 5½ cm. The heart rate varied from 65 to 75 beats per minute. There was a slight degree of sinus arrhythmia and an occasional premature contraction. The first sound at the apex was long, dull, and somewhat reduplicated, and the second sound was weak, the pulmonic being greater than the aortic. There were no murmurs. The peripheral arteries were somewhat thickened, and the pulse was of medium quality with an occasional intermission. The blood pressure was systolic 120, and diastolic 65.

The abdomen and extremities were negative.

The Electrocardiogram. Fig. 3 shows portions of the electrocardiogram obtained by the standard leads, on a standardization of 10 mm. being equivalent to 1 millivolt. The impulse is seen to originate in the normal sinus area at a rate of about 65 per minute. The *P–R* conduction is normal. The *Q–R–S* complexes show the following features: they are of low voltage, the maximum being 0.45 mv.; the conduction time is prolonged upward of 0.12 second, and they are markedly slurred and notched. The *P* and *T* waves assume a normal directional course except in the third lead, where the *T* wave is diphasic.

The moderate sinus bradycardia and slight arrhythmia suggested the possibility that vagal influence was the underlying cause of the interventricular conduction disturbance. I have attempted, therefore, the removal of such influence by exercise. Fig. 4 is a part of the tracing in the second lead obtained after the patient was made to hop on one leg about 30 times in 1 minute. It will be noted that the only change is an increase heart rate at the expense of a shortened diastolic period. The *Q–R–S* complexes retain the same abnormal features as before exercise, except that their voltage is somewhat increased. One premature ventricular contraction is seen not followed by any compensatory pause, and the succeeding complexes were of the same abnormal type as before.

After a rest period sufficient to return the rate to the previous level, an attempt was made to see what effect vagal stimulation would have on the abnormal *Q–R–S* complexes. Carotid sinus pressure was employed for that purpose. Fig. 5 is a tracing in the second lead obtained on right vagal

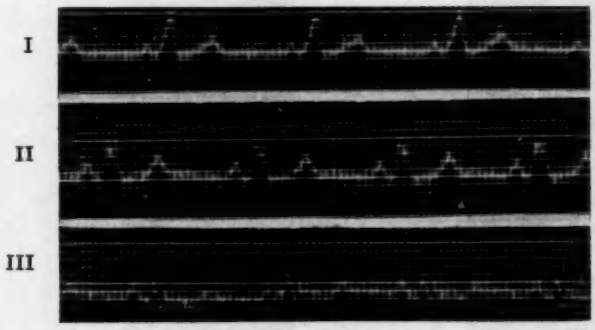

FIG. 3.—Rate about 55, slight sinus arrhythmia. *P–R* interval normal. There is an increase in the *Q–R–S* conduction time to 0.12 second with marked slurring and notching, and low voltage, the maximum being 0.45 millivolts. The *T–R* interval is 0.44 to 0.53 seconds.

stimulation. A slowing of the heart to about 60 per minute for about two cycles is seen, followed by a ventricular premature contraction with a compensatory pause of about 0.8 second. The next *Q–R–S* complex appears perfectly normal, the conduction time being 0.06 second. This is again followed by a series of the usual abnormal *Q–R–S* complexes on continuing the right vagal stimulation.

FIG. 4.—Obtained after exercise. The *Q–R–S* conduction time remains at 0.12 second, with slurring and notching. One ventricular premature contraction is seen, not followed by any compensatory pause, and with no change in the character of the subsequent complexes.

Left vagal stimulation, on the other hand, yielded different results. Fig. 6 is a tracing in the second lead obtained by such stimulation. Four of the usual abnormal complexes are seen with a gradual increase in the *T–R* interval. This is followed by a series of normal ventricular complexes, at a rate of about 55 per minute, with marked sinus arrhythmia. The *Q–R–S* conduction time is about 0.06 second, with no notching or slurring, and about 1 mv. This persisted as long as left vagal pressure was maintained. The *T* waves are the same with the abnormal as with the normal *Q–R–S* complexes.

Discussion. The electrocardiogram presented in this case, unmodified, corresponds to the so-called "arborization block" of Oppenheimer and Rothchild.[12] The *Q–R–S* complexes are prolonged beyond 0.1 second, notched, are of low voltage and there is the absence of the

FIG. 5.—Second lead of tracing obtained on right vagal pressure: The *T-R* interval does not exceed 0.56 second in any cycle. The *Q–R–S* complexes show the same abnormalities as in Fig. 3, Lead II. One ventricular premature complex is seen, followed by a compensatory pause of 0.8 second, and this is followed by a normal *Q–R–S* complex.

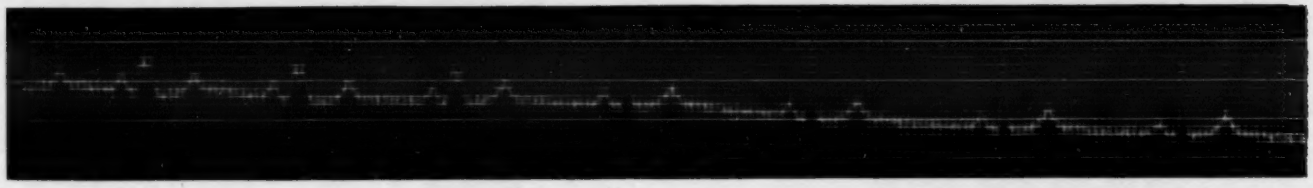

FIG. 6.—Tracing obtained on left vagal pressure: The first four *Q–R–S* complexes are of the abnormal type, with *T–R* intervals of 0.4, 0.5 and 0.5 seconds respectively. Following the fourth complex, there is a series of normal complexes persisting as long as vagal stimulation was done. The *T–R* intervals are 0.64, 0.72, 0.76, 0.72, 0.68, 0.72 and 0.88 seconds respectively. Only part of tracing is shown.

typical character of the *T* wave found in complete bundle-branch block, which is opposite in direction to the major deflection.

We need not discuss here the correctness of or objections to the term "arborization block," which has been done amply by such authorities as Wilson and Hermann[13] and Lewis.[14] Suffice it to say that the ease with which the normal complexes were restored in this case would tend to prove the contention of the latter authors that the *Q–R–S* conduction disturbances in such cases are dependent upon a delay in one of the main branches of the bundle rather than in the arborizations and muscle mass. Depending upon the amount of delay, there is a corresponding variation in the algebraic summation of the dextro- and levocardiogram resulting in the abnormality.

That normal complexes were so easily restored by the vagal reflex is also sufficient proof that the condition was not dependent in this case upon any anatomic pathology. The interesting question then is "what caused this conduction disturbance, and how did vagal stimulation relieve it?" Although we must employ theoretical conceptions to answer it, we have sufficient evidence in the electrocardiogram to prove that either vagal inhibition or fatigue is responsible for the condition—most likely the latter.

That vagal inhibition may effect the bundle branches was shown in the preliminary discussion of this paper, and the conception of its partial interference with the passage of the impulse along the right bundle branch, is plausible. Left vagal stimulation which would theoretically increase inhibition along the left branch might thus have a tendency of producing normal *Q–R–S* complexes, as the impulse would reach the muscle masses of both ventricles simultaneously, even if more slowly. There are, however, two objections to this theory. (1) Adequate proof has not yet been brought forward to show the direct effect of each vagus nerve upon the corresponding bundle branch. (2) Assuming that the normal ventricular complex produced in this case by left vagal inhibition was a direct effect of that nerve upon the left bundle branch, we should expect some auriculoventricular block at the same time. This can be easily understood when we realize that regardless of where the retardation of the impulse coming from the auricles to the ventricles takes place—whether in the supraventricular area or lower down—the end result should be the same. In this case, however, there was no prolongation of the *P–R* interval during the period when normal ventricular complexes were produced. This fact alone is sufficient to discard this theory.

The second theory, namely that of fatigue of one of the branches causing the disturbance, finds more support. It also explains the relief obtained by left vagal stimulation.

If we represent the period of electrical inactivity of the conducting apparatus of the ventricles by the *T–R* interval, starting at the end of the *T* wave and ending at the inception of the *R* wave, and if we

study carefully this interval from cycle to cycle, we find that when its duration is less than 0.64 second, it is followed by an abnormal Q–R–S complex. Thus, the minimum T–R interval in Fig. 3 is 0.44 second and the maximum 0.52 second, and the Q–R–S complexes are all abnormal. In Fig. 4, these intervals are greatly shortened and the respective Q–R–S complexes remain definitely aberrant, even with the marked increase in the heart rate. Examining Fig. 5, which is the tracing obtained by right vagal pressure, we find that none of the T–R intervals reaches 0.64 second. One notable exception in this tracing is a ventricular premature contraction, followed by a long compensatory pause of 0.8 second, and the succeeding Q–R–S complex is normal. This in itself proves that giving the ventricular conducting apparatus more time to rest, the Q–R–S complex following such rest is normal. It is also noteworthy to find that a similar premature contraction in Fig. 4, not being associated with a compensatory pause, is not followed by a normal complex. The best proof of this contention is found in Fig. 6 obtained by left vagal stimulation. The T–R interval in the first three cycles associated with abnormal Q–R–S complexes are 0.4, 0.5, and 0.5 of a second respectively. Following these, and caused by vagal stimulation, there is a definite slowing of the heart to about 55 beats per minute and the T–R intervals are 0.64, 0.72, 0.76, 0.72, 0.68, 0.72, and 0.88 of a second respectively, each of which is followed by a normal Q–R–S complex. In other words, longer rest restored normal functional activity. This clearly indicates that fatigue is the underlying cause of the disturbance. Judging from these figures, we find that as short an interval as 0.08 second more than the maximum T–R interval of 0.56 second, which is not followed by a normal complex, is sufficient to restore normal rest to the interventricular conducting apparatus in this case.

We may conclude, then, that it was not the direct vagal effect on the bundle branches which produced the results in this case. It was merely the slowing of the impulse formation in the sinoauricular node, under left vagal stimulation, giving increased rest to the conducting apparatus of the ventricles, and it was this increased rest which restored normal conduction in this case.

Summary. 1. Bundle-branch block, complete and partial, may be functional in origin, caused predominantly by vagal inhibition and fatigue.

2. Restoration of normal Q–R–S complexes in such cases may be accomplished by removal of vagus inhibition where vagal effect is the underlying cause, and by local rest where fatigue is the cause.

3. A paradoxical case is reported where left vagal stimulation apparently removed rather than caused such block.

4. The underlying functional disturbance in this case was apparently fatigue of one of the bundle branches which was sufficiently relieved by increased vagal slowing to permit normal bundle-branch conduction.

5. Abnormal Q–R–S complexes occurred after as long a rest as 0.56 of a second, and normal complexes were restored by additional rest of 0.08 of a second.

NOTE.—I am indebted to Miss Marcella F. Hughes of the Electrocardiographic Laboratory of the New York Post Graduate Hospital for the preparation of the electrocardiograms in Figs. 1 and 2 for publication.

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WHAT HAPPENS EVENTUALLY TO PATIENTS WITH HYPERTHYROIDISM AND SIGNIFICANT HEART DISEASE FOLLOWING SUBTOTAL THYROIDECTOMY?*

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TREMENDOUS strides have been made in recent years in the care of patients suffering from hyperthyroidism, particularly in those cases with gross evidence of cardiac involvement. As a result of the intro-

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duction of basal metabolism determinations into clinical work, the refinements in surgical technique, the use of iodin in pre-operative treatment and especially the clinical recognition of previously undetected types of hyperthyroidism, many patients now respond most satisfactorily to treatment who, in the past, either would have succumbed to operation or would not have been recognized as suffering from thyroid disease. As Lahey well expressed it, there is now practically no "thyrocardiac" who cannot be treated surgically with a high degree of safety and hopefulness.[1] Much has been written about clinical recognition of these "masked" cases,[2,3,4,5,6,7,8] demonstrating that the immediate effects of proper treatment are most extraordinary. Many patients with moderate or advanced heart failure or angina pectoris who have been refractory to all the ordinary therapeutic procedures have regained compensation and have been restored to normal or fairly normal activities following a subtotal thyroidectomy. It is the purpose of this study to see what the ultimate condition of these patients may be, and to ascertain whether the marked improvement is temporary or permanent. It is further hoped to distinguish the rôle played by the thyroid gland in the production of the cardiac symptoms from that due to other independent concomitant factors. In other words, we were desirous of studying the status of as many of these "thyrocardiacs" as possible years after operation. Particular attention was directed to the changes in the blood pressure, size of the heart, murmurs and irregularities of the heart. Finally, we were interested to learn if the improvement was permanent, and, in general, what the subsequent health of such patients might be.

Types of Cases Included. This study was confined to 69 cases of hyperthyroidism showing evidence of gross disturbance in the cardiovascular apparatus. In every instance a subtotal thyroidectomy was performed. There were 51 females and 18 males. The average age was 50.7 years when they first came under observation, and the entire group was followed for an average of 4.5 years. The preoperative basal metabolic rate before administration of Lugol's solution averaged +51.1 per cent; after operation the average metabolism of the entire series was +4.8 per cent.

Peabody[9,10,11] and others[12,13] have shown that the basal metabolism in severe grades of heart disease is variable, frequently being normal, but in some instances being elevated to +20 per cent or even more. In heart disease, generally, Peabody states[9] that "The rise in basal metabolism is neither a constant nor particularly significant feature." We feel that metabolism readings found repeatedly in the neighborhood of +20 to +30 per cent in a patient with heart disease are suggestive of an underlying hyperthyroidism.

In this series all patients with congestive heart failure and angina pectoris as well as hyperthyroidism were included. In the former group the majority had objective evidence of circulatory congestion

such as subcutaneous edema, engorged liver or moisture in the lungs. In a small number there was sufficient dyspnea and cardiac enlargement to make it clear that congestive failure, although not marked, was present. Auricular fibrillation was present in many of these cases, but in none was it the only criterion of cardiac involvement. An analysis of these cases quickly shows that most of them had various forms of heart disease in addition to hyperthyroidism. In fact, there were 15 patients with definite and 4 with questionable mitral stenosis of rheumatic origin. Two cases had aortic insufficiency, 1 being due to syphilis and the other to rheumatism; 35 had hypertension. In 30 cases persistent auricular fibrillation was present, transient in 14 other cases. There were 6 instances of auricular flutter, 1 of bundle branch block, 1 of Adams-Stokes attacks resulting from long sinus pauses and 1 of acute pulmonary edema. Some of the cases naturally fell into more than one group, as a patient could have hypertension, auricular fibrillation and mitral stenosis in addition to hyperthyroidism.

It is interesting that having limited our cases to those with congestive or anginal heart failure, all of the cases, with rare exceptions, presented evidence of other forms of heart disease in addition to hyperthyroidism. Hyperthyroidism alone did not account for the cardiovascular changes in the great majority of the cases. Other factors, such as hypertension, mitral stenosis, etc., combined with hyperthyroidism to produce the abnormal cardiac states in the patients, and these findings persisted after the hyperthyroidism was relieved, although the symptoms may have either improved or disappeared. The above features and the fact that congestive heart failure is extremely rare in young people with hyperthyroidism makes us concur with the prevailing conception that hyperthyroidism itself does not produce heart failure.[1,3,6,14,15] Of the entire group of 69 patients there were 43 who had objective evidence of congestive heart failure of varying extent. Those with mild congestive failure had merely râles in the lungs in addition to dyspnea; the more marked had gross anasarca. There were 9 who had typical angina pectoris, and 2 of these had had definite attacks of coronary thrombosis a short while before subtotal thyroidectomy. All the remainder had appreciable dyspnea and cardiac enlargement apart from the common complaints found in hyperthyroidism, such as palpitation, weakness, nervousness and sweatings, although they did not show evidence of peripheral congestion. Of this latter group 6 had persistent auricular fibrillation and 5 paroxysmal auricular fibrillation. It is obvious that this group does not include the ordinary type of exophthalmic goiter or those cases of hyperthyroidism in which the heart shows no appreciable evidence of involvement.

Observations on the Blood Pressure. As has been shown by Hurxthal,[16] there is only slight change in the blood pressure following

subtotal thyroidectomy in cases of hyperthyroidism. In his study there was an average drop of 10 mm. in the systolic pressure and a rise of 7 mm. in the diastolic pressure in a group of 46 cases of toxic goiter followed for 12 months after operation.

In the cases studied here similar lack of change was noted. The average readings of 43 of our cases were systolic 153 mm. and diastolic 81 mm. before operation, and systolic 156 mm. and diastolic 85 mm. 3.3 years after operation. The average metabolism determinations at these two times were +45.3 and +5.9 per cent. The group of 20 cases with a normal blood pressure before operation showed an average increase of 10 mm. in systolic pressure after 3.3 years (Table 1). The cases varied considerably as far as the blood pressure readings were concerned. In some instances it was distinctly higher after operation than before, but more often it was slightly lower. It was very rare that a well-marked hypertension before operation entirely disappeared after the basal metabolism was brought to normal by surgery. When this did occur observations made months or years later generally showed return of the hypertension.

TABLE 1.—FOLLOW-UP OBSERVATIONS ON BLOOD PRESSURE.

	Number of cases.	Aver. systolic blood pressure, mm.	Aver. diastolic blood pressure, mm.	Aver. basal metabolic rate, per cent.
Hypertensive:				
Pre-operative	23	179	89	+43.9
Postoperative (3.3 yrs.)		177	94	+ 5.1
Nonhypertensive:				
Pre-operative	20	123	71	+46.9
Postoperative (3.3 yrs.)		133	75	+ 6.9
Total:				
Pre-operative	43	153	81	+45.3
Postoperative (3.3 yrs.)		156	85	+ 5.9

There was a strikingly large number of cases of hypertension among these patients with hyperthyroidism and gross cardiac involvement. There must be more than an accidental relationship between hypertension and hyperthyroidism. It is unlikely that hyperthyroidism itself produces hypertension, inasmuch as restoring the metabolism to normal and relieving the patients of most, if not all, of their symptoms did not significantly alter the blood pressure level. Furthermore there is no relationship between the level of the blood pressure and the level of the metabolism reading either in the same individual at different times or comparing one case with another. Contrariwise, hypertension does not produce hyperthyroidism, for most hypertensives have normal metabolic rates and normal thyroid glands. May it not be that the constitutional type of individual who is likely to get one condition is also apt to get the other, and in this way both necessarily occur frequently together?

If this is true, one may expect to find hypertension occurring with undue frequency in later life in patients who had hyper-

thyroidism with a normal blood pressure in early life. This is borne out by the slight but definite rise in the blood pressure 3.3 years after operation in patients who had pre-operative normal readings.

Hypertension and hyperthyroidism afford frequent practical problems in diagnosis, as many features are common to both conditions. At times it is difficult to tell clinically whether there is any additional hyperthyroidism in a patient who has hypertension, and occasionally even after the results of metabolism determinations are available, the diagnosis still may be in doubt.

Changes in the Size of the Heart. Roentgen ray changes in the size of the heart have been carefully studied in the Lahey Clinic by Hurxthal, Menard and Bogan.[17] They found that the size of the heart in toxic goiter was not appreciably different than in nontoxic goiter when similar age groups were compared. In fact, in their study no relationship could be found between the duration of the disease and the size of the heart. These authors merely call attention to the size of the heart tending to be larger in older patients with coincident cardiovascular disease. Parkinson and Cookson,[18] on the other hand, found cardiac enlargement in 45 per cent of 130 clinical cases of "goiter causing symptoms." They believed that the duration of the symptoms was a factor in producing enlargement. From an experimental point of view, there is reliable evidence that hypertrophy of the heart occurs in animals following the administration of thyroid substances.[19] A study of heart weights in patients dying of hyperthyroidism was made by McEachern and Rake.[20] They found that in 27 such cases 16 had cardiac hypertrophy. It cannot be concluded, however, that even in these cases enlargement was due to the hyperthyroidism because a concomitant independent form of heart disease is so frequently present.

In this series of cases there were 10 in which Roentgen ray examination of the heart was made before operation when the metabolism was elevated, and afterward when it was approximately normal. Several other cases were omitted because the difference in the internal transverse diameter of the thorax in the two examinations was too great to make accurate measurements of the heart size possible. The changes in the size of the heart were, on the whole, insignificant. There was only one instance in which the transverse diameter of the heart changed more than 1 cm.; in this case there was a diminution in that diameter of 1.7 cm. In all the others the changes were within the margin of error of the method. The average size of the heart showed a total transverse diameter of 14.3 cm. before operation and a transverse diameter of 14.2 cm. after operation. The internal transverse diameter of the chest averaged 26.2 cm. before and 26.5 cm. after operation (Table 2). Although these data are rather meager, they are suggestive that in "thyrocardiacs" with gross cardiac involvement, the heart size

will tend to be slightly to moderately increased, that the size does not change to any great extent following operation, and finally that the enlargement itself is due to the coëxistent independent cardiovascular disease rather than to the hyperthyroidism.

TABLE 2.—AVERAGE ROENTGENOGRAPHIC MEASUREMENTS OF THE HEARTS OF 10 HYPERTHYROID PATIENTS WITH HEART DISEASE.

	B.M.R., %.	M.R.	M.L.	Tr.	G.V.	Int. diam.	Tr. %, Int. diam.
Just before subtotal thyroidectomy	+41.8	5.1	9.2	14.3	6.4	26.2	54.5
Twelve weeks after operation	− 7.0	5.2	9.0	14.2	6.4	26.5	53.6

Changes in Cardiac Murmurs. There were 27 instances in this series of 69 cases in which specific notation of murmurs was made before and after operation. In all these systolic murmurs of varying intensity were present before operation. In 16 instances the systolic murmur disappeared after operation. In 8 it became less intense and in 3 it remained unchanged. There were 8 of these same 27 that had an additional diastolic murmur. In 6 instances this was apical in origin and the character of the murmur was typical of mitral stenosis. Three of these were first noted after operation. There were 2 cases with aortic diastolic murmurs, 1 of which first appeared after operation. Of 42 cases in which no specific mention of murmurs after operation was made, 27 before operation had only systolic murmurs, 7 had systolic and diastolic murmurs and 1 had only a diastolic murmur at the apex. There were only 7 of the entire 69 who showed no murmurs before operation.

A systolic murmur in these cases, for the most part, was found both at the apex region and at the base of the heart. Although these cases had heart disease besides the element of hyperthyroidism, the frequent disappearance or diminution in intensity of the systolic murmurs makes it clear that hyperthyroidism itself may be wholly or partly responsible for these murmurs. Moreover, the diastolic murmur of mitral stenosis can easily be overlooked, especially during the period of active hyperthyroidism. Furthermore, the ability to hear a diastolic murmur for the first time after operation indicates the importance of careful auscultatory examination when the metabolism has reached normal levels.[14]

Changes in the Irregularities of the Heart. Irregularities of the heart in hyperthyroidism are very common. Auricular fibrillation, especially in the transient form, is particularly frequent.* Of these 69 cases there were 32 which had permanently established auricular fibrillation, many of which, no doubt, previously had transient

* See Bibliography, Nos. 1, 2, 3, 5, 7, 8, 14, 21, 22, 23, 24, 25.

attacks of the same arrhythmia. There were additional 12 cases which showed only paroxysmal auricular fibrillation. Inasmuch as a paroxysm of auricular fibrillation is of common occurrence a day or so after subtotal thyroidectomy, cases having such attacks as the only disturbance of rhythm were not included in this group. Ten of the cases of paroxysmal auricular fibrillation never gave any evidence of recurrent attacks after leaving the hospital. There was 1 instance in which transient auricular fibrillation recurred at varying times several years after the operation, but the metabolic rate in this case was found to be elevated and there was additional clinical evidence of mild recurrent hyperthyroidism. One final case had a single transient spell of auricular fibrillation 3 years after operation. This patient had hypertensive heart disease and, because a metabolic rate determination was not made at this particular time, it was uncertain whether or not she had recurrent hyperthyroidism. In a word, there was no instance in which recurrent auricular fibrillation took place in which it was known that the metabolism was normal.

Among the group of 32 patients that had persistent auricular fibrillation there were 24 who were examined at different intervals after leaving the hospital so that one could tell whether or not the fibrillation persisted. Of 11 patients who also had mitral stenosis the irregularity remained established in 10; in the eleventh, normal rhythm was established by the use of quinidin sulphate. Unfortunately this patient suffered an attack of hemiplegia that same day and was for a while desperately ill. Although she made an excellent recovery and the heart has remained regular for almost 2 years, our enthusiasm for the use of quinidin in the presence of mitral stenosis has waned. It is interesting that in none of the 11 patients who had mitral stenosis and persistent auricular fibrillation as well as hyperthyroidism, did the heart return to normal rhythm spontaneously after thyroidectomy. Of the remaining 13 cases the heart spontaneously became regular shortly after operation in 5 without any further medication and normal rhythm has remained for years. One was regularized by the use of quinidin and in the other 7 the auricular fibrillation continued and quinidin was not employed. Of these latter 7 cases, 6 had hypertension and the remaining 1 had a blood pressure of 145 systolic and 80 diastolic with an enlarged heart. No doubt if quinidin had been used in these cases, a regular rhythm might easily have been restored. Some have been followed as long as 8 years and it is known that once the heart became regular transient or permanent fibrillation did not recur during this time.

In summarizing our experiences with auricular fibrillation, one may predict that if the hyperthyroidism is adequately controlled by surgery and the metabolism established at a normal level, cases with transient auricular fibrillation may be expected to be entirely

free from such attacks in a great majority of instances.[1,2,6,14,22,24,25] Those who have persistent fibrillation and who also show mitral stenosis will almost invariably continue with auricular fibrillation. In some of the others a normal rhythm will be established spontaneously within 1 to 4 weeks after operation. Those in whom regularization does not occur after 1 month will probably continue to show auricular fibrillation indefinitely. For the most part it seems that the irregularity persists because there is present an independent and additional type of heart disease such as hypertension, cardiac hypertrophy or coronary artery disease, although in some the hyperthyroid state still may be lurking despite the partial thyroidectomy. Quinidin may be employed in cases which continue to show irregularity due to auricular fibrillation 1 month after the operation, but we believe there is considerable risk if mitral stenosis is present. It may be added that it is futile to give quinidin for auricular fibrillation before operation and inadvisable for a week or two after operation. In the first instance auricular fibrillation will probably recur promptly, if it disappears at all; and in the second instance, there will be found some cases in which the auricular fibrillation persists for a week or so before spontaneously changing to a normal rhythm.

Paroxysmal auricular flutter occurred in 6 instances in this series.[23] In 5 cases there was no return of such attacks after operation, whereas in 1 case 4 weeks after subtotal thyroidectomy the patient had an attack of auricular flutter which lasted 5 days. The metabolism at this time, however, was +18 per cent. There were no instances of persistent flutter in this entire group.

There were only 6 cases in which it was noted that extrasystoles of one sort or another were present. Of these there were 3 with ventricular premature beats, 1 with auricular premature beats and 2 with nodal beats. No doubt there were other cases in which premature beats occurred which were not noted. Despite this, it is our general impression that extrasystoles are not common in hyperthyroidism. This has been the experience of other writers.[23,26,30]

Two cases showed an irregularity of the heart due to well-marked sinus pauses. In 1 of these occasional standstill of the heart for from 5 to 8 seconds occurred; this produced fainting and momentary unconsciousness. The heart rate in this case was in the vicinity of 40, and the clinical picture that resulted resembled Adams-Stokes disease, although there was no true auriculoventricular heart block. There were 2 cases that showed first degree heart block or delayed auriculoventricular conduction. In 1 of these the *P–R* interval was 0.23 second before operation and became normal (0.2 second) postoperatively. The second patient had a *P–R* interval of 0.22 second before operation and it was unchanged after operation. Delayed auriculoventricular conduction in cases of toxic goiter has been reported by various writers.[14,23,26,27] There was

1 instance of block of one of the branches of the bundle of His in our group.

In summary, it may be said that almost any type of cardiac irregularity may occur in "thyrocardiacs" but that the only disturbance that is truly characteristic of hyperthyroidism, and which may frequently disappear after the hyperthyroidism is relieved, is auricular fibrillation, transient or permanent. Sinus pauses may well be due to direct pressure of the thyroid gland on the vagus nerve or on the carotid sinus, for in the case mentioned above both lateral lobes of the thyroid were found at operation to lie posteriorly and behind the trachea in a position that could easily produce such pressure. Most of the other irregularities could result from the accompanying independent heart disease and need not be directly related to the hyperthyroidism.

Effect on Angina Pectoris and Congestive Heart Failure. The association of angina pectoris and hyperthyroidism has been referred to in recent years.[4,28] The finding of 9 such cases in this series indicates that this association is by no means rare. Although females far outnumber the males among hyperthyroid patients in general, in this group with angina pectoris there were 6 males and 3 females. It is also interesting that at least 7 had typical attacks of angina at rest. This is not at all surprising when it is appreciated that the added drive on the heart in hyperthyroidism is going on constantly. Two of these patients went through typical attacks of acute coronary thrombosis and were subsequently and successfully operated upon for the hyperthyroidism. Although it is difficult to make a comparative analysis between the blood pressure level in these thyroid patients with angina and our "thyrocardiacs" without angina, it seems that hypertension is not as prominent a feature in the former as in the latter. In fact there were several instances in which the blood pressure was perfectly normal.

The clinical improvement that occurred in this group of patients with angina was most striking. The average duration of anginal symptoms in these patients before operation was 31 months. In every instance the attacks either completely disappeared or they recurred very rarely and were much milder. The average length of time these patients were observed postoperatively was 20 months, the interval varying from a few months to about 4 years.

It is our opinion that all these patients were suffering from angina pectoris as a result of the same causes that produce angina in nonhyperthyroid cases. We believe that they have coronary artery disease of varying degrees. In hyperthyroidism the accompanying elevated metabolism merely serves as an added burden so that even while at rest in bed these patients might be compared to a normal individual who is performing some effort. Angina pectoris has been produced following the administration of thyroid medication to patients with myxedema who previously had no such at-

tacks.[29] One might say that in the hyperthyroid state these patients were, in effect, exercising 24 hours a day although they were constantly in bed. They might need no additional effort, therefore, to bring on attacks of angina pectoris; in fact, only minor changes in their nervous or physical states might do so. The operation merely relieved them of the added burden on the circulation accompanying the elevation of the metabolism to +35 or +50 per cent, but the underlying process in the coronary arteries, although possibly mild, still remained. It would, therefore, be expected that following the relief subsequent to thyroidectomy, anginal symptoms might still be produced, only now requiring much greater insults, either physical or mental, to produce them and that the progression of the coronary disease would continue with subsequent liability to increase in attacks of angina pectoris. We believe it extremely unlikely that hyperthyroidism itself would cause angina pectoris in a heart otherwise normal, especially one with normal coronary arteries.

In this group of cases there were 43 patients who had physical evidence of varying degrees of congestive heart failure. On the average, one might classify the failure as being moderate to severe. There were many who had general anasarca with peripheral pitting edema, markedly engorged liver, hydrothorax and dyspnea at rest; 11 had mitral stenosis, 1 questionable mitral stenosis and 21 hypertensive heart disease.

There were 2 postoperative deaths. One died within 24 hours after operation in a thyroid crisis during the days before the introduction of Lugol's solution therapy. The other was an instance in which improvement on iodin treatment was so gratifying that both the patient and his physician refused to follow our advice to have a subtotal thyroidectomy performed. It was done some weeks later when the optimum time for surgery had passed. In this case the thyroid condition had been overlooked for 2 years, and the diagnosis of thyroid heart disease, when it was made by one of us, really was accepted with great reluctance on the part of the family physician. In fact, in the entire series of 69 patients there have been no postoperative deaths in cases that were directly under our control since the introduction of Lugol's solution. In most cases the improvement occurred with pre-operative treatment following the use of Lugol's solution and the customary procedures employed in treating heart failure. In these the operation served to maintain the gain previously obtained and enabled such patients to resume approximately normal activities. In others, further improvement took place after operation. It was very striking, except for rare instances, that all evidence of congestive heart failure had disappeared within 2 or 3 weeks following operation.

This group of patients suffering from congestive failure was extraordinary from the fact that so few have died during subsequent

years. The follow-up study of cardiac patients with congestive failure in hospitals no matter what type is analyzed, generally shows a high mortality within 2 years. Here only 6 have died, excluding the 2 postoperative deaths. The average length of life of these 6 patients was 2.5 years after operation. They all had been markedly improved in the meantime. Of the remaining 35 patients the present status of 4 is not known; the average postoperative survival of the others is 49 months. There are 11 who have been alive over 5 years, 6 of whom have survived more than 7 years. Only 8 of these have been followed less than 2 years. The actual length of life after operation, although of itself impressive, is not quite as important as the fact that in almost all instances these patients have been able to resume their ordinary duties.

There are some general impressions that one cannot avoid after a study of any large group of "thyrocardiacs," such as has been undertaken here. Patients with various forms of heart disease and hyperthyroidism seem to have an extraordinary tenacity for life. Even during the months and years when the thyroid element has been entirely overlooked they carry on better and live longer than one would ordinarily have expected. When they are in advanced heart failure with general anasarca they seem to hold on to life months longer than other patients with heart disease, and it seems that no matter how sick they are, they are still amenable to proper treatment and considerable recovery may be anticipated.

An experience with a single case in this series was quite illuminating. This woman, aged 61 years, had been bedridden for many months with general anasarca. She had been treated with the greatest care by competent consultants and heart specialists. On admission here, cardiac enlargement, auricular fibrillation and moderate hypertension were found. There was no evidence of valve disease. She showed frequent digitalis coupling with nausea on 0.1 gm. of digitalis once or twice a day. The metabolism reading while she had massive generalized edema was +23 per cent; a repeat examination was +18 per cent. On Lugol's solution there was marked improvement and it was decided to perform a subtotal thyroidectomy, notwithstanding the fact that it seemed unlikely that she had true hyperthyroidism. The situation seemed otherwise hopeless and we thought some good might come from subtotal thyroidectomy even if a normal gland were removed. This operation was done and, as a result, she got rid of all the edema, lost 50 or 60 pounds in weight, became ambulatory and felt better than she had for some years, despite the persistent hypertension. The pathologic report was "normal thyroid gland." This, to be sure, was the only instance of the entire series in which the pathologist's report indicated a normal thyroid gland. She continued in good health for 3 years, then gradually developed moderate congestive heart failure again, and finally died 4.5 years after the operation.

The long control period before surgery was undertaken makes it quite unlikely that the marked improvement after operation could have been a coincidence.

An experience like the one cited above makes one suspect, at least, that the removal of a part of the thyroid gland which grossly and microscopically appears normal may be helpful in the treatment of heart failure. Additional evidence that tends to support this view is available. There are patients who have auricular fibrillation who show no other evidence of heart disease nor of thyroid or other disease of the body. Such patients have a normal basal metabolism, no valvular disease or hypertension and are little incapacitated by the auricular fibrillation. We have seen 10 or 12 such cases. They all more or less look alike, have a moist skin and other clinical features resembling those seen in hyperthyroidism but without exophthalmos or an enlarged thyroid gland. Occasionally, years later, such a patient may have an elevated metabolism. Wishart[30] has observed 6 of these cases and has reported 1 of them in detail. He concludes that auricular fibrillation (or flutter) may be the earliest detectable sign of thyrotoxicosis in patients with normal basal metabolic rates who later develop Graves' disease. There are reports[31,32] in which thyroidectomy was performed and the gland found to be hyperplastic when the metabolism was normal.

Morris and Troell,[32] in a study of 17 cases of "thyrotoxicosis" with basal metabolic rate within normal limits, found by microscopic examination that the thyroid gland was hyperplastic in 13, with nodular goiter in the remaining 4.

Symmers,[33] moreover, has reported clinical and postmortem observations on 6 cases of "idiopathic cardiopathy," that is, cases in which there was enlargement of the heart, but without valvular, pericardial, arterial, renal or pulmonary causes. At autopsy, however, all of them showed gross and microscopic changes in the thyroid gland; 5 of the 6 were increased in size; microscopic examination of all revealed a "hyperplastic thyroiditis." The basal metabolic rates of these patients were not reported.

The inference from all this is that the metabolism test, even when within normal limits, may not absolutely rule out active hyperthyroidism, or the finding of a normal thyroid gland may not mean that the gland has been functionally normal. Finally, it is possible that partial removal of a normal thyroid gland may be helpful in patients who have either angina pectoris or the congestive type of heart failure.

Summary and Conclusions. 1. A follow-up study was made of 69 "thyrocardiacs" in whom subtotal thyroidectomy was performed. All of these cases before operation had gross evidence of congestive or anginal heart failure. There were 2 postoperative fatalities, and of the remainder the average length of follow-up was 4 to 5

years. Six patients died since the operation after an average survival of 2.5 years. These 6 had been restored either to normal health or to resumption of moderate activities.

2. Forty-three cases had objective evidence of congestive heart failure; 9 had angina pectoris, 2 of whom had had coronary thrombosis; 15 had definite mitral stenosis and 4 had questionable mitral stenosis; 2 had aortic insufficiency (1 was luetic, 1 rheumatic); 35 patients had hypertensive heart disease.

3. The average basal metabolic rate before operation was +51.1 and +4.8 per cent after operation. The average preoperative blood pressure was 153 mm. systolic and 81 mm. diastolic; postoperative, 165 mm. systolic and 85 mm. diastolic. The heart size was practically unchanged as a result of operation. The average pre-operative transverse diameter of the heart in 10 cases was 14.3 cm. and postoperatively it was 14.2 cm. All but 7 of the 69 showed some type of heart murmur before operation.

4. In 27 cases specific notation was made concerning the presence of murmurs before and after operation. All these cases had systolic murmurs and 8 had diastolic murmurs. In 16 instances a pre-operative systolic murmur disappeared, in 8 it became less marked and in 3 it remained unchanged. Of the 8 diastolic murmurs 6 were due to mitral stenosis and 2 to aortic insufficiency. Three of the former and 1 of the latter first became audible postoperatively.

5. Of 32 cases that had established auricular fibrillation, 24 were adequately reëxamined. Of these 11 had mitral stenosis and in none of these did the auricular fibrillation spontaneously disappear. Of the remaining 13, 6 reverted to normal rhythm after operation and the cardiac rhythm remained regular for years. There were an additional 11 cases that showed paroxysmal auricular fibrillation. In practically all instances these paroxysms did not recur after the patients left the hospital.

Our experience with quinidin in these cases indicates that it is useless to employ it pre-operatively for auricular fibrillation and dangerous to give it postoperatively to those patients with mitral stenosis and auricular fibrillation. It is best given a few weeks after operation to those without mitral stenosis in whom auricular fibrillation is still persisting.

Six cases of paroxysmal auricular flutter occurred in this series. These attacks disappeared permanently in all but 1 of the cases. In the latter instance there was a single return of this arrhythmia associated with some evidence of persisting hyperthyroidism.

Sinus pauses occurred in 2 patients who were both permanently relieved following operation. There were 2 instances of delayed auriculoventricular conduction, 1 of which became normal after subtotal thyroidectomy.

Extrasystoles were relatively uncommon; there were only 6 instances of this irregularity in the group studied.

6. The great rarity of congestive heart failure in young patients with hyperthyroidism and the almost uniformity of other forms of heart disease (mitral stenosis, hypertension, coronary artery disease, etc.) in those with significant cardiac embarrassment makes it probable that hyperthyroidism is rarely the sole cause of heart failure.

7. The follow-up study of these cases showed that not only was there marked immediate improvement following operation in the various evidences of circulatory embarrassment such as congestive heart failure, angina pectoris and disturbing irregularities of the heart, but the improvement was extremely well maintained.

8. The occurrence of striking improvement following subtotal thyroidectomy in a patient with advanced congestive heart failure, in whom the thyroid gland was normal, suggests that this operation may be useful more generally in the treatment of various forms of cardiac disease.

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CLINICAL AND PATHOLOGIC STUDIES IN A CASE OF PURE LIPOID NEPHROSIS.*

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The existence of pure lipoid nephrosis as an entity independent of glomerulonephritis is denied by many authorities on diseases of the kidney. Its extreme rarity is admitted even by those observers who claim for it a separate identity. The studies here reported offer evidence to support the position that lipoid nephrosis can occur without demonstrable clinical or pathologic signs of glomerulonephritis. Furthermore, the case record is of interest because the patient was a young adult, whereas most reported instances have been in children; she died relatively early in the course of the disease (9 weeks after onset), without having developed a single clinical indication of glomerulonephritis; and at necropsy the evidence of chronic extrarenal disease which might have accounted for the "nephrotic syndrome" was absent. After careful histologic study of the kidneys including recently advocated staining methods, the glomeruli were regarded as free of the inflammatory or proliferative

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changes of nephritis, although the tubular elements were strikingly altered.

It is necessary in the beginning to indicate exactly what is meant in this report by the term pure lipoid nephrosis. We conceive the term to designate a disease of undetermined etiology characterized clinically by persistent marked albuminuria, massive edema, lipemia and low serum protein; pathologically by kidneys which show lipoid degeneration of the tubules but no inflammatory reaction in the glomeruli insofar as histologic studies can determine. The clinical manifestations of renal irritation or of insufficiency of the kidney as an excretory organ are uniformly absent in lipoid nephrosis. Absent also are cardiovascular disease and chronic infection with amyloid degeneration of organs.

Those who maintain the identity of pure lipoid nephrosis admit that the clinical phenomena may be matched to the smallest detail in both positive and negative aspects by certain stages of glomerulonephritis. The line of differentiation, they contend, is found in the histologic characteristics of the glomerulus: Insofar as the kidney is concerned, lipoid nephrosis is a degenerative process of the tubules, and the glomerulus, unlike that of nephritis, is not detectably involved.

The foregoing position was maintained against opposition by Fahr[1] whose pathologic material and treatment of it have been recognized the world over. The same conclusion is reached by Leiter[2] in a recent exhaustive review of the subject of nephrosis. Both recognize the great rarity of the disease. Epstein[3] originated the conception widely held that the disease is primarily metabolic rather than renal; that in some obscure way the serum proteins are changed and filtered out by normal glomeruli; that the most striking clinical phenomenon, the edema, is due to the tremendous drop in blood protein and consequent loss of colloid osmotic pressure; and that the lipemia is a secondary phenomenon which, if effective, would have regained for the blood a fluid-retaining force.

While most observers agree that the edema of lipoid nephrosis is due to the loss of serum albumin, proof is lacking that the cause of this loss is a change in the protein rather than a change in the glomerulus through which it is filtered. Bell[4] most recently has consolidated the position of those who believe that all so-called cases of pure nephrosis show some degree at least of glomerulitis, and that the disease is one of the glomerular capillaries. Bell's position is based on: (1) The extremely close similarity to lipoid nephrosis in all respects of the nephrotic type of glomerulonephritis where disease of the glomerulus is obvious; (2) the preponderant evidence[5] to date that the urine albumin of nephrosis is identical with that of the serum and therefore must be excreted by abnormal glomeruli; and (3) with special staining technique he has satisfied

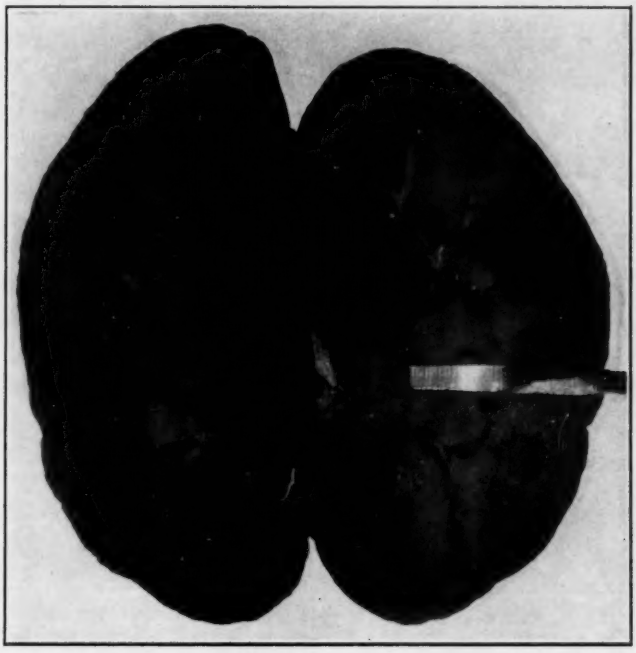

FIG. 1.—The kidney of lipoid nephrosis. It is swollen with marked widening of the cortex.

FIG. 2.—Pure lipoid nephrosis. Scarlet R stain for fat without counterstain. Complete absence of fat droplets in the glomerulus. Tubules show prominent lipoid material. Photomicrograph × 175.

FIG. 3.—Pure lipoid nephrosis. There is moderate intertubular edema. A few of the tubular cells can be seen to contain vacuoles. Intratubular casts are prominent. Hematoxylin-eosin stain. Photomicrograph × 175.

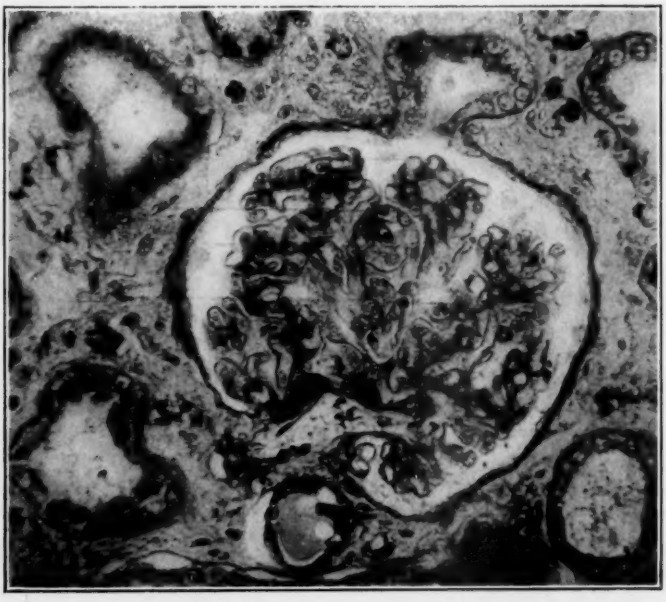

FIG. 4.—Pure lipoid nephrosis. Glomerular tuft showing no cellular proliferation or obstruction of capillary loops. Azan carmin stain. Photomicrograph × 400.

himself that in "pure" lipoid nephrosis there is detectable thickening of the capillary basement membrane and an increase in the number and size of the endothelial cells of the glomerular tuft. The primary disturbance in both nephrosis and nephritis, according to Bell, is an injury to the glomerular capillary by some toxic agent. If little or no reaction occurs in the capillaries a pure nephrosis develops; a moderate reaction produces nephritic symptoms.

Pathologic evidence opposed to the contention that all pure nephrosis cases show glomerulonephritis of some degree is offered in the following case report:

Case Report.—E. G., an American housewife, aged 28 years, complained when first seen at home of 3 weeks of increasing weakness and swelling of the face and extremities. The symptoms began without known cause 9 weeks after the normal termination of her first pregnancy. Midway in the pregnancy her doctor had found a transient albuminuria. No urinalyses had been made in the last 3 weeks before delivery or in the puerperium until she was brought already edematous from her farm home in upstate Pennsylvania to Philadelphia.

The only disease of any consequence in the patient's past had been chorea at the age of 12 years, recurring subsequently in mild abbreviated form on 4 or 5 occasions. The tonsils had been removed at 20 years of age following one of the recurrences. There had been no cardiac symptoms, and shortly before marriage the patient had taken out a small life insurance policy without difficulty.

Physical examination showed edema of the eyelids, lower trunk and extremities, but no excess fluid in the serous cavities of the body. There was no evidence of infection and the temperature was normal. The eyegrounds were negative. The lungs were clear and the heart of normal size and action, with an apical systolic blow well transmitted. Blood pressure readings averaged 115 systolic and 75 diastolic. The abdomen was negative.

Laboratory Findings. The patient refused hospitalization at first and laboratory study of blood and urine was not as complete as desirable. All urine specimens were of specific gravity between 1020 and 1040. When heated, the urine solidified with the coagulated albumin, one quantitative albumin estimation was reported as 50 gm. per liter. Hyalin and granular casts were present in profusion, but microscopic or chemical (benzidin test) hematuria was not detected. The urine contained doubly refractile lipoid bodies.

The blood Wassermann reaction and blood count were negative. Blood urea nitrogen (later, after 3 days of urea therapy) was 21 mg. per cent, or barely above normal. Blood serum protein was 4.5 per cent by refractometer, below the level at which edema appears. Blood cholesterol figures were not obtained but the serum was distinctly milky. Kidney function tests proved impossible.

Treatment and Clinical Course. The patient was diagnosed as a case of lipoid nephrosis and treated with high-protein diet, limited fluid and salt, thyroid extract and diuretics. Anorexia and increasingly frequent vomiting spells interfered with the diet, but in the intervals, over a period of 4 weeks, the protein intake varied between 70 and 100 gm. daily. The daily urine output varied between 300 and 800 cc. Of the diuretics used to combat the oliguria, ammonium chlorid was not tolerated, urea in 24-gm. daily dosage brought on almost no diuresis. Salyrgan intravenously brought about a transient flushing on 4 of 6 occasions.

The course of the disease was slowly downhill from the beginning, with

no remission worthy of the name. Watery diarrhea, probably caused by intestinal edema, occurred from time to time. A month after she was first seen the patient developed a fever and signs of a cellulitis in the waterlogged tissues of the flank, whereupon she was forced to enter the hospital. The end came as a result of the erysipelas-like infection and exhaustion 9 weeks after onset.

Necropsy (*U. of Pa. '32–151*) (W. T. R.). External examination reveals marked edema, particularly of the abdomen and lower extremities. The right thigh, buttock and flank are cyanotic and the skin is indurated, giving the appearance of cellulitis or erysipelas.

The important internal changes are limited to the *kidneys*. The right weighs 250 gm., the left, 300 gm. The capsule strips easily leaving a smooth surface, yellow in color but free of hemorrhages. The cortex measures 7 to 10 mm. in width and is bright yellow in color in contrast to the medulla which is dusky red, due to hyperemia (Fig. 1). A small wedge-shaped infarct is found in the right kidney. It appears to be recent in origin.

Microscopically the glomeruli are normal in size and there is no recognizable cellular proliferation of either epithelium or endothelium. The capillary tufts are all unobstructed and contain blood. No hyalin fibers are demonstrable by McGregor's stain.[6] In the capsular spaces there is a network of protein material. None of the cells of the glomeruli contain droplets of lipoid as revealed by the Scarlet R stain (Fig. 2). There is moderate intertubular edema and the tubules themselves are dilated. Many contain casts and cellular débris. The epithelium lining the tubules shows in many places fine vacuoles within the cytoplasm (Fig. 3). The Scarlet R stain reveals these to be lipoid droplets. There is no structural change in the bloodvessels.

Several connective-tissue stains were made: Van Gieson, anilin blue, and orange G, one counterstained with fuchsin and another with azan carmin by the technique of McGregor.[6] In these sections neither the capsule of Bowman nor the capillary basement membrane showed any thickening. There is no overgrowth of connective tissue (Fig. 4).

Other internal alterations which should be mentioned are the presence of 1600 cc. of milky yellow fluid within the abdomen and a small vegetation measuring 4 or 5 mm. located on the mitral valve of the heart. Microscopically this shows fibroblastic proliferation and a few lymphocytes. On one side the endothelium is lost and a small thrombus was found. No bacteria are present. Postmortem cultures of the subcutaneous tissues in the area of cellulitis, of the heart's blood and peritoneal fluid yielded only an organism of the colon type, undoubtedly a postmortem contamination.

Comment. Although certain clinical data in this case are perforce not complete, we feel that sufficient evidence was obtained to fulfill the rigid criteria for the diagnosis of pure lipoid nephrosis, with pregnancy as a possible exciting factor. In the histologic examination Heidenhain's azan carmin modification of Mallory's anilin blue stain was used according to the technique followed by Bell in his study of nephrosis.[4]

If the view that the glomerular capillary change is primary is correct (*i. e.*, that it is in reality a nephritis), the alterations which permit the escape of albumin are not detectable in this instance by our present-day histologic methods. It is conceivable that the process represents only a change in glomerular capillary permeability for which as yet demonstrable morphologic equivalents are lacking.

Summary. Data are presented from a case which bore the clinical features of lipoid nephrosis, and in which the kidneys on careful study showed lipoid degeneration of the tubules but no morphologic evidence of glomerulonephritis.

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THE TREATMENT OF PRIMARY DYSMENORRHEA. WITH ESPECIAL REFERENCE TO ORGANOTHERAPY.*

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Before such an organization as this, dedicated as it is to the study of the treatment of disease, no apology should be necessary for the consideration of one of the most difficult therapeutic problems in gynecology. For obvious reasons, and particularly because this affection is commonly relegated to the category of "minor gynecological disorders," it is one of the everyday problems in the work of the general practitioner as well as the specialist. The patients themselves would scarcely acquiesce in its designation as a minor disorder, for it is, in the aggregate, the cause of more suffering and invalidism than many conditions dignified by the appellation of "major."

While the earlier literature is full of articles upon primary dysmenorrhea, almost nothing of solid nature can be crystallized out from them, for they are almost altogether of a speculative nature, both as to the etiology and the therapeutic measures recommended. Only within the past few years, with the intensive study of the physiology of the female reproductive system, has there appeared a hope of solving the problem of the mechanism and the treatment of this extremely common ailment.

* Read at annual meeting, American Therapeutic Society, Baltimore, May 17, 1932.

With the secondary type of dysmenorrhea, associated as it is with some definitely recognizable pelvic abnormality, an explanation of the menstrual pain is usually evident, and the indication for treatment clear. With the primary variety, and it is with this alone that we are concerned in this paper, the pelvic organs are characteristically normal, although the patient may suffer excruciating menstrual pain. Most often, although not invariably, this begins 1 or 2 days before the actual menstrual onset, and ceases after menstrual bleeding is well established, usually after the first day. As is well known, the affection is most often seen in young unmarried women or in married nulliparæ.

While this paper is concerned chiefly with the therapeutic aspects of this problem, these are so utterly dependent upon etiology that the latter must at least be touched upon, the reader being referred, for a full discussion of this question, to a recent paper by the present author, in collaboration with S. M. R. Reynolds. The time-honored view, of course, is that the dysmenorrhea is the result of an obstruction to the exit of menstrual blood, most often because of a kink associated with anteflexion. There are many reasons why this can not explain most cases, not the least being the frequent observation of severe dysmenorrhea without anteflexion or obstruction of any kind and, vice versa, of very sharp anteflexion with no pain whatsoever.

Equally unsatisfactory is the evidence for the importance of hypoplasia of the uterus as a cause of primary dysmenorrhea. For example, a large proportion of dysmenorrheic patients date the onset of the menstrual pain, not from puberty, but from a period several, or perhaps many, years later. This observation is hard to check up with the essential importance of a primary hypoplasia of the organs, present from birth. Furthermore, the uterus of the dysmenorrheic patient is often quite normal in size.

Not so easily dismissed, however, are two other factors, the constitutional and the psychogenic. The first of these will unquestionably explain a certain proportion of cases, just as it will explain the production or exaggeration of other subjective symptoms. Here we apparently have to deal with a lowering of the threshold of pain, so that the normally slight menstrual discomfort is magnified into an actual dysmenorrhea. Most often the constitutional depravity is obvious, or is readily enough revealed by the proper examination. It may be a severe anemia, or tuberculosis, diabetes or any one of many other systemic disorders. In the strict sense, therefore, the dysmenorrhea in such patients is secondary rather than primary, although the pelvic organs themselves are normal. Certain it is that many such patients can be relieved of the dysmenorrhea by correction of the underlying cause, with the institution of proper hygiene, exercise and other indicated measures.

Even more important, although much more difficult to evaluate,

is the psychogenic factor which is undoubtedly concerned in many cases of primary dysmenorrhea, as with other functional disorders. Indeed, there are some gynecologists who believe that all cases are of psychogenic origin, a generalization to which I can not subscribe. Such authors lay much stress upon Freudian factors, but explain other cases as due to such causes as mental shocks at or near the menstrual period, with the subsequent development of a conditioned-reflex mechanism; suggestibility, as when a girl has been reared in the same household with a dysmenorrheic mother; a feeling of repulsion at the offensiveness of the menstrual discharge, and so on.

I am personally convinced that the psychogenic factor is the important one in a considerable number of cases, but I feel just as strongly that it can not explain all. Every gynecologist must encounter patients in whom no such factor can be brought out, who perhaps are of a very phlegmatic temperament, and who apparently possess normal bodies and minds. Psychiatrists with whom I have talked tell me that the assumption of a universal psychogenic factor in the explanation of primary dysmenorrhea would be far-fetched.

Still another factor remains to be considered, that of a possible rôle of certain endocrinopathies. Dysmenorrhea may at times, of course, be encountered in patients with well-defined endocrine disorders, but most often it is not. There have, of course, been many speculative attempts to explain this affection on an endocrine basis, but until very recently nothing of a scientific nature had been contributed. Recent investigations upon the question of the hormonal regulation of uterine contractility have yielded the first results which seem applicable to the clinical problem of dysmenorrhea. The very nature of the pain in these cases would, of course, suggest an origin in an exaggerated or disordered contractility of the uterine musculature. The recent investigations of Knaus, Reynolds and a number of others throw much light upon this problem. They are fully discussed in the recent paper of Novak and Reynolds, based on the latter's studies on the variations in uterine contractility under various conditions, and under the influence of certain hormone factors.

To summarize these only very sketchily, Reynolds has found, by an ingenious method of study, that (1) uterine muscle exhibits a normal rhythm of contraction; (2) all uterine contractions disappear after castration; (3) they are restored by the injection of folliculin; (4) the folliculin-produced contractions are inhibited by the injection of progestin or of the urine of pregnant women; (5) the normal excitant of uterine contractility is the follicle hormone, while the corpus luteum principle, progestin, is an inhibitor.

We have attempted to apply these results to the problem of primary dysmenorrhea, always, of course, bearing in mind the possible contributory rôle of psychic and other such factors, as already

discussed. The corpus luteum normally begins to retrogress a day or two before menstruation; in other words, at just the time the dysmenorrhea commonly begins. The natural assumption, therefore, would be that it is the rather abrupt withdrawal of the inhibitory progestin influence which allows full play to the stimulating folliculin. The latter, according to the studies of Frank and others, is present in the blood in increasing amounts from the end of one menstrual period to the beginning of the next. After the formation of the corpus luteum, and especially during the premenstrual period, when it reaches the maximum, the characteristic folliculin effect upon the uterine musculature is inhibited by the progestin produced by the corpus luteum. The withdrawal of this inhibiting effect is apparently responsible for the onset of uterine contractility, and this, in some cases, is characterized by pain.

The above statements are based upon, and I believe are in accord with, the physiological facts which I have summarized. The sequence of physiological events, however, occurs in all women during the normal menstrual cycle, and yet only a comparatively small proportion suffer pain. For this, two explanations suggest themselves. One is that the exaggerated uterine motility is registered as pain only in those women whose pain threshold is lowered by constitutional, psychogenic or other factors. The other is that there must be in some women an imbalance between the two antagonistic hormonal principles, either quantitative or chronologic.

This point is still beyond proof, but I believe that such physiologic investigations as those above mentioned point to a hormonal disorder of uterine contractility as at least the immediate cause of primary dysmenorrhea.

Treatment. The management of cases of primary dysmenorrhea must obviously be directed toward two objectives: (1) the treatment of the attacks themselves and (2) the permanent relief of the condition. These will be discussed in at least a brief and summarizing fashion.

The Dysmenorrheic Attack Itself. When confronted with a patient suffering the often excruciating pains of primary dysmenorrhea, the physician's immediate concern is with the relief of pain. The first injunction to be borne in mind, perhaps, is to refrain from the administration of morphin, for not a few women addicts date their affliction from the use of morphin for this condition. Alcohol should be prescribed with equal caution. While of undoubted benefit, in the form of either whisky or of some of the alcohol-laden proprietaries, there is danger in its use. Cases of moderate severity are, of course, often relieved by the simpler analgesics, such as codein or the coal-tar products, together with rest in bed, hot applications and hot drinks.

From what has been said as to the causative rôle of exaggerated and painful muscle contraction, the administration of antispasmodic

drugs would seem to be called for. The best of these, in my experience, is atropin sulphate, as I discussed in a paper published 17 years ago. This is administered by mouth in doses sufficient to cause mild saturation symptoms. An average dosage is $\frac{1}{120}$ gr. of the sulphate every 4 hours, beginning from a day to several days before the period, depending on the usual time of onset of pain. In a large proportion of cases, great and often complete relief is obtained.

However, such physiologic considerations as I have discussed in this paper suggest that a more rational and perhaps more effective antispasmodic may now be available. The biologic inhibitors of uterine contractility, on the basis of laboratory investigations, are progestin and the luteinizing principle of the urine of pregnant women. The former is not available for human use, but the latter is, even commercially. Its use I believe to be rational, and the short experience I have thus far had with it is most gratifying. I shall not stress the point now, for the method is too new to speak of results, especially since we are dealing with a disorder where the subjective factor may so readily mislead us.

For those who may be interested in such clinical experimentation, however, I may say that an intramuscular injection of 100 rat units of the substance (Antuitrin S, of Parke, Davis & Co.) is given 1 or 2 days before menstruation, this being repeated 1 or 2 days, depending on the severity and usual duration of the pain. This plan, as I shall again emphasize, constitutes only a part of the intelligent treatment of dysmenorrhea.

Measures Looking to Permanent Relief. The time-honored view that primary dysmenorrhea is cured by the first pregnancy is, in the main, correct, although some exceptions are encountered. Marriage, however, cannot be prescribed as complacently as can medicine.

The factor of hypoplasia, considered so important by some gynecologists, and undoubtedly present in some cases, can, I believe, be helped by the use of theelin. Indeed, I know of no other intelligent method of accomplishing this. The administration of theelin to animals brings about marked overgrowth of the uterus, with hyperemia. With full allowance for the uncertainties and probable inadequacy of dosage for the human, the hypodermic use of folliculin is indicated in primary dysmenorrhea. The administration of 50 rat units on alternate days for 6 days, beginning just after menstruation, is the usual plan I have followed. In other words, all the injections are given during the follicular phase of the cycle.

The resort to cervical dilatation, so common in the past and even at the present day, is of course based on the older idea of the obstructive etiology of dysmenorrhea, now rather generally abandoned. That it has been effective in at least a fraction of the cases permits of no doubt, but the doubt arises in trying to determine the mechanism of its effect. Is it entirely psychic, or is it based upon

a real virtue in the dilatation? One cannot be dogmatic, but there can be little question that in many cases the operation is a form of psychotherapy, at times successful, although not infrequently only temporarily. This is not a radical statement, for it can be made of many other measures which have been used for this condition and, as a matter of fact, there is no doubt that many cases of the "psychogenic" variety are cured without either drugs or surgery.

With reference to this last group the physician should never forget that the psychic factor must always be borne in mind, so that a careful history should be obtained, especially as to the time of onset of the dysmenorrhea, and a possible correlation of this event with a psychic trauma of one sort or another. As already stated, I do not believe that such an etiology can be demonstrated with the constancy claimed by some authors, but not infrequently it can. Furthermore, whatever the cause of the first attack may be, there is always the possibility that the factor of fear may lead to recurrence and perpetuation of the symptom. This subject is as involved as are many other psychiatric problems, but a good history, interpreted along broad and sane lines, will usually lead to a proper evaluation of the individual case.

Every such gynecologic consultation should be an educational one from the standpoint of the patient, the physician taking the time to reassure her as to the significance and normality of the menstrual function, of the fact that it is commonly associated with very little discomfort, that it should cause little or no interference with her usual activities, and so on. I have always felt that in many instances the mothers of dysmenorrheic young girls are in greater need of such education than the patients themselves, for too often the girl at puberty is coddled into the belief that the menstrual period is a time of semi-invalidism and physical discomfort, requiring abstention from exercise of all sorts and almost a species of segregation. This picture is not overdrawn, although in recent years a far healthier attitude is gradually coming to prevail.

Finally, only an additional word need be added as to the importance of general constitutional building-up and measures of general hygiene. This topic need not be elaborated, although it is an important one. I have repeatedly seen dysmenorrhea disappear entirely, with no direct treatment of the pelvic disorder in itself, by encouraging the patient to get interested in outdoor sports, and engendering in her mind a pride in her physical development.

Summary. The treatment of primary dysmenorrhea, still a baffling problem in gynecology, has been rendered difficult because of our ignorance of the factors concerned in its etiology. Constitutional and psychogenic factors, among others discussed in the paper, would appear to be of prime importance in many cases. Evidence has been brought forward, chiefly from recent physiologic investigations, to indicate that the immediate cause of the pain is

an exaggerated contractility of the uterus, manifested as pain if the pain threshold is lowered, or if there is an actual imbalance between the two hormones which appear to regulate this contractility. These are folliculin, the normal stimulant of uterine excitability, and progestin, the normal inhibitor. While we cannot, of course, discuss these relationships in a precise or quantitative way, the clinical characteristics of primary dysmenorrhea, on the one hand, and physiologic studies on the other, both indicate the importance of this hormonal factor in the production of the pain.

The treatment of the attack itself, aside from such customary measures as rest, hot applications and analgesics, may rationally include the administration of antispasmodics, such as atropin. Even more intelligent would seem the administration of biologic uterine antispasmodics, the one suggesting itself being the luteinizing principle obtained from the urine of pregnant women. This substance, readily available, has been shown to be, like progestin, a powerful inhibitor of the rhythmic contractility of the uterine muscle.

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DEFECTIVE COLOR VISION AND ITS HANDICAPS IN MEDICINE.*

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George Wilson, of Edinburgh, was stirred to a study of color blindness by the mistakes made by students in his laboratory in judging the colors of chemical precipitates. Among his cases there were 5 physicians. One of them confessed that "red in the lips, cheeks, nose, roses, gooseberries, inflammations and the like looks blue to me! On one occasion I could not tell a blue line of water color drawn across my finger from blood." Another admitted that "a rose, the lips, a ruddy complexion and the face of a man discolored by nitrate of silver are to my eyes absolutely the same."[1]

Wilson ventured to say from his experiences that for some of these physicians there could not be such things as "scarlet fever" or "cyanosis." Their defect rendered them incapable of recogniz-

* Aided by a grant from the J. Ewing Mears Research Fund.

ing these conditions. The truth of this assertion was well confirmed in the course of the present work.

Scope of Investigation. Since inspection is one of the chief methods of observation in medicine, whether at the bedside or in the laboratory, and much of inspection is dependent on color perception, it struck us as well worth while to investigate whether or not defects in color perception did materially affect the interpretation of clinical findings.

In this paper the term "color blind" will be strictly avoided in designating those individuals with subnormal color sense. The term should be reserved for those who cannot see any colors at all. In other words, to those who cannot see in the solar spectrum but different gradations of white, gray and black. Such individuals are rare. Between them and those with normal color sense there is a group (from 4 to 10 per cent of the population, according to different authors) who have varying qualitative and quantitative degrees of color sense loss. We will refer to these as having a defective color sense or simply as "color defective." As a generic term this fits our present purposes better than the subdivision into dichromat, trichromat, etc.

Method and Material. The material for this study consisted of 70 members of the junior class of the medical school. In order to sort out the men who had any difficulty in color sense, the entire group was asked individually to read the Ishihara plates.[2] These plates are modeled somewhat after the original Stilling plates. One of us (L. M. T.) tried the relative merits in a large group of individuals of the Ishihara test, the Holmgren woolens, the Williams lantern and the Jennings test in detecting defects in color sense. The first of these was found to be the most sensitive. The Ishihara test has also the advantage of eliminating from consideration those who are merely "color ignorant" as the subject is required only to read numbers and not to give the names of colors. Clark[3] considers it the most successful of the various color blindness tests.

Of the 70 who were given the test, 61 read the plates correctly; 9 read incorrectly 2 or more plates, that is, 12.8 per cent of individuals with color sense defects were found in this group.

The 9 who did not pass the test were then asked to perform the following: (1) Titrate an unknown acid mixture, using phenolsulphonephthalein as an indicator; (2) determine the percentage of phenolsulphonephthalein in 2 urine specimens by matching them against standards of known percentage; (3) identify Gram-negative and Gram-positive organisms in separate smears; (4) describe the appearance of acid-fast organisms in 2 slides, 1 with methylene blue, another with Bismarck brown as counterstains; (5) identify a polymorphonuclear neutrophil, basophil and eosinophil in 3 slides; (6) name the colors of the solar spectrum as seen through a spectroscope.

TABLE 1.—ANALYSIS OF COLOR TESTS IN 9 DEFECTIVES AND 2 NORMALS.

Subject.	Titration of acid mixture with phenolphthalein as indicator.		Matching 2 urine spec. against P.S.P. standards.		Identification of							Naming of spectrum colors.
	Unknown. Cc.	Titration. Cc.	First. Per cent.	Second. Per cent.	Gram-pos. organisms.	Gram-neg. organisms.	Acid-fast bacilli with methylene bl. as counterstain.	Acid-fast bacilli with Bismarck brown as counterstain.	Polymorph. neutrophil.	Polymorph. eosinophil.	Polymorph. basophil.	
A . . .	1.1	1.1	50 to 60	20 to 25	Correct	Called Gram-pos.	Blue bac. on blue field	Black bac. on br. field	Neutrophil	Basophil	Basophil	Red, yel., gr., blue, pur.
B . . .	1.2	1.2	50 to 55	20 to 25	Correct	Called Gram-pos.	Deep blue bac. on lt. blue field	Blue bac. on golden br. field	Neutrophil	Eosinophil	Basophil	Red, yel., gr., blue, deep blue.
C . . .	1.0	1.0	55	25	Correct	Correct	Dark blue bac. on lt. blue field	Blue bac. on straw field	Basophil	Basophil or neutrophil	Basophil	Red, yel., gr., pur.
D . . .	1.1	1.1	50 to 55	20 to 25	Correct	Called Gram-pos.	Dark blue bac. on blue field	Pink bac. on yellow field	Neutrophil	Probably an eosinophil	Basophil	Red, or., yel., gr., blue, violet.
E . . .	1.3	1.3	50 to 55	20 to 25	Correct	Called Gram-pos.	Entire field and bac. look blue	Dark brown bac. on br. field	Neutrophil	Neutrophil	Basophil	Red, yel., gr., blue.
F . . .	1.1	1.1	50	20	Correct	Called Gram-pos.	Purple bac., blue field	Dark brown bac. on orange field	Neutrophil ?	Neutrophil	Basophil	Red, yel., or., gr., pink, blue.
G . . .	1.2	1.2	50	15	Correct	Called Gram-pos.	Field and bac. look blue	Violet bac. on orange field	Neutrophil ?	Neutrophil	Basophil	Br., yel., red, blue, violet.
H . . .	1.5	1.5	40	10	Correct	Called Gram-pos.	Blue bac. on blue field	Blue bac. on orange field	Basophil	Neutrophil	Eosinophil	Yel., blue.
I . . .	1.3	1.3	30	10	Called Gram-pos. (dark blue)	Called Gram-neg. (green color)	Blue bac. on blue field	Blue bac. on orange field	Eosinophil or neutrophils	Eosinophil	Lymphocyte	Red, yel., gr., blue.
J . . .	1.4	1.4	60	25	Correct	Correct	Lt. red bac. on bl. field	Red. bac. on brown field	Neutrophil	Eosinophil	Basophil	Red, or., yel., gr., bl., pur.
K . . .	1.3	1.3	55 to 60	25 to 30	Correct	Correct	Red bac. on blue mucus	Red bac. on brown field	Neutrophil	Eosinophil	Basophil	Red, or., yel., gr., bl., pur.

The test objects were all typical examples of their kind. The tests were carried out at the same place, at approximately the same time of the day, and with an equal amount of illumination. Any communication between the subjects was prevented. Six students of the same class in school with normal color vision, who had made no mistakes reading the Ishihara plates, were given the tests and used as controls. The results are detailed in Table 1. For the sake of brevity only 2 normals (J and K) are included in the tabulation.

Results. The 9 students who had failed in reading the Ishihara plates also failed in the tests. In the control group an occasional mistake was made in the titration of the acid mixture, which was subsequently corrected when the titration was repeated. The same opportunity for repeating titrations was afforded the color defective group. Occasionally one of the normals would underestimate or overestimate the phenolsulphonephthalein percentage by 5 or 10 per cent, or would fail to name the orange in the spectral colors. No other mistakes were made by the normal group.

Titrations by the color defective group were invariably correct. In matching phenolsulphonephthalein specimens, mistakes were frequently made. There was greater underestimation among those with a severe grade of defective color perception (G, H and I). Those with a mild degree of defect made correct or nearly correct matches. One man stated that it was impossible for him to match the specimens, as the standards and the specimens were of different color.

The identification of Gram-positive organisms was made correctly by all the men. All but 2 of the defective group called the Gram-negative organisms positive; 1 of these stated that he could tell the difference between the two kinds because the Gram-positive organisms appeared dark blue, the others green.

The entire group failed to describe correctly the appearance of acid-fast bacilli, if methylene blue was used as the counterstain; no contrast whatever was detected between the organism itself and the surrounding matter. Whenever Bismarck brown was used as the counterstain the contrast was evident and the organism recognized. One man (D), who had seen the organism dark blue against a blue background, saw it in its right shade of pink when Bismarck brown was used.

In the identification of granulocytes, but 2 individuals made correct observations. There was particular difficulty in the identification of eosinophils, as we anticipated.

The naming of the spectrum colors gave us a rough qualitative idea of the color defect of these individuals. It can be seen readily that of the subnormal group, the last 4 probably had the greatest degree of color defect.

To extend the scope of this investigation, each individual was

asked to state some of the difficulties he experienced in color perception during his stay in medical school. The results were interesting. Three men stated they experienced difficulty in detecting skin lesions, especially the mild exanthematous type. Several cases of scarlet fever with a frank rash were demonstrated, but not recognized. A jaundiced patient appeared tan to 1 man, who stated he could be sure of seeing jaundice only when he could contrast it against the white of the sclera. The same individual also had trouble in recognizing cyanosis. Cyanosis, he stated, appeared deep red to him. Once he was shown a patient with carcinoma of the stomach, who was slightly wasted and was told to note the pasty, grayish appearance of the man's face. Although this was obvious to others, the man's color to him was a normal tan.

One man had great difficulty in estimating hemoglobin with a Dare apparatus. The standards, he said, were not strong enough. He stated that he realized he had a defect in color vision, but that he was careful to have his worked checked by a classmate. This classmate was later tested and found to be as color defective as himself. In volunteering information as to other color defective individuals in his class, he pointed out one that he considered particularly severe. This man was tested and found normal. Another student was shown a blood smear of pernicious anemia and instructed to note the difference in the staining qualities of the erythrocytes. Some, he was told, stained light red, whereas others were bluish gray. He countered by saying that all the erythrocytes he saw looked bluish gray and none light red.

One had been shown a culture of Streptococcus viridans and could not understand why the organism was called green producing, since the material did not look green to him.

Nearly all of the subjects had difficulty in identifying the tubercle bacillus. This had led to mistakes in the examinations and a few of the men had, in some courses, been given low grades because of their inability to identify this organism. Some had devised ingenious ways of circumventing the difficulty. When doing a test involving the detection of a certain color, one man prepared solutions with a known amount of the chemical for which he was testing. Then he would set them aside and use them as standards while going through with the titration of the unknown.

One of the students (H) became so confused in the coloring of his anatomic drawings that he had a classmate point out to him the colors of the different pencils. He then gave to each one a separate number, made out a table of the colors and its corresponding numbers and always referred to it before coloring any section of his drawing.

Comment. It is evident that color defective perception is an important variable in the estimation of laboratory and clinical

results. Many otherwise unexplained discrepancies between results in different laboratories handling portions of the same material may be explained in terms of difference in color perception. Many of the complicated chemical tests depend for their interpretation upon a keen color sense that sometimes even the normally endowed individual fails to possess from lack of proper education. Likewise, the recognition of certain types of tissue depends upon their staining reaction, and defects in color perception may affect this recognition. The fact that laboratory work is performed, in many instances, by female technicians is fortunate, as it is known that color defective perception is rare in that sex. It might, of course, be argued that in comparing scientific data, a margin of error must, in the last analysis, be considered, owing to the variable "personal equation." A large share of the variability of this equation can, however, be ascribed to differences in color perception.

Although slight degrees of defective color sense should not be set forth as a bar to the study of medicine, the individual with such a defect should be well appraised of it in order that he may make the proper allowance and not engage in lines of work in which he would be distinctly handicapped.

Individuals with the degree of color sense loss as found in G, H and I should be barred from performing laboratory work or specializing in dermatology or in any other specialty in which accurate observation by inspection is essential.

The color defective has, however, as a compensation for his shortcomings in differentiating colors, a high degree of ability in the discrimination of fine brightness values. Many of these individuals see better in the dark than those with normal color vision. Little[4] mentions a Philadelphia publishing firm which prized one of its color defective engravers very highly for his superiority over workers with normal color sense in transcribing accurately light and shade effects.

This quality, which often leads the color defective astray when identifying colors, should prove advantageous in roentgenology, particularly in fluoroscopic work and the reading of Roentgen ray films. This specialty, therefore, would seem singularly well suited to individuals with the more severe grades of defective color vision.

Summary. 1. Seventy junior medical students were tested for defective color vision. Nine were found defective (12.8 per cent).

2. The 9 students with defective color sense performed tasks requiring color discrimination. All made mistakes, some showing a greater degree of color defect than others. Six students with normal color vision were used as controls.

3. A few of the students had a marked degree of defect in color sense that led to errors in their clinical work.

4. Individuals with markedly defective color sense should be dissuaded from lines of work requiring accurate observation and

encouraged to engage in work calling for technical rather than diagnostic skill.

5. On account of the tendency for good discrimination of brightness values, roentgenology would seem an appropriate specialty for those with a markedly defective color sense.

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ANNULAR PANCREAS.

A COMPILATION OF 40 CASES, WITH A REPORT OF A NEW CASE.

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ANNULAR pancreas is a comparatively rare developmental anomaly, in which the second portion of the duodenum is encircled by a ring of pancreatic tissue. It has both a clinical and anatomical importance. A search of the available literature revealed 39 previously reported cases to which the author desires to add another:

Case History (136089).—A married woman, aged 37 years, was admitted to the San Francisco Hospital, October 14, 1930, complaining of pain in the abdomen for 3 days. She had not felt well for the past few months, had lost 6 pounds in weight, was tired, had been drinking alcoholics heavily, and had noticed that the whites of her eyes had become yellow. Three days previous to admission she was suddenly seized with acute severe pain in the pit of her stomach, not accompanied by nausea or vomiting. The pain continued, and on the following day she vomited a large amount of chocolate-colored fluid which contained flecks of bright red blood, and her stools were black. She had not eaten since the acute attack and stated that she "ached all over."

Family History. Her father died at 82 of "cirrhosis;" her mother of cancer of the uterus at 47. One brother drowned, 2 brothers and 6 sisters were living and well.

Personal History. The patient had the usual childhood diseases, also diphtheria at 32. She had been married twice, but had separated from each husband; both had been heavy drinkers. She was operated upon for appendicitis in 1907, and for adhesions in 1908. In 1909 she had leucorrhea and pelvic inflammatory disease, following which both tubes and one ovary were removed. Her appetite had always been irregular, and she had had

indigestion and pain in the stomach after eating, off and on for years, with frequent periods of constipation. In 1924 she became nauseated, vomited blood and was operated upon for gastric ulcer. The gall bladder was removed at this time because it contained stones. For the past several months she had been short of breath, and noticed swelling of her ankles and morning puffiness below the eyes.

Physical Examination. A medium-sized, well-developed and nourished woman of about 35 years of age, weighing about 125 pounds, was seen in a semistuporous condition, She looked ill. Her pupils reacted poorly to light; the scleræ were definitely icteric, and the conjunctiva moderately injected. The lips were dry and cracked, the tongue beefy and coated, the breath had a distinct acetone odor. The heart was of normal size, the sounds regular, 80 per minute, of good quality with an apical systolic murmur. The blood pressure was 140/74 mm.; the respiratory rate 20. A few crackling râles were heard at the right lung base posteriorly. There was hyperesthesia and moderate rigidity of the abdominal wall, more marked on the right side superiorly, no masses or organs palpable, no visible peristalsis. Reflexes were normal, but there was a generalized hyperesthesia. The temperature was 97.2° F.

Laboratory Data. Urinalysis: Negative for glucose, heat and acetic test for albumin boiled solid; occasional erythrocytes and leukocytes and one granular cast seen. Blood count: Red blood cells, 5,200,000 per c.mm.; white cells, 13,850, with 86 per cent polymorphonuclears, and 14 per cent lymphocytes. Blood Wassermann test, negative.

Course. By the third day she appeared to be in a uremic stupor. The blood urea was 300 mg. per cent, the icterus was more marked. The possibility of a common duct stone or of hepatitis was considered. The following day her condition was grave, with occasional bleedings from the mouth and impending uremic state. The icteric index was 75; the van den Bergh test showed an immediate direct reaction qualitatively and 31 units quantitatively.

On the 7th day she was very weak, with gums bleeding, temperature 99.2° F., pulse 104, and respirations 40 per minute. She became very dyspneic, and expired at noon.

The *clinical diagnosis* was alcoholism, starvation acidosis and uremia. The possibilities of acute hemorrhagic nephritis, leaking peptic ulcer, common duct stone, and hepatitis were considered.

Autopsy (No. XXXIV–51). The examination was performed by Dr. E. M. Butt, to whom the author is indebted for the opportunity to study this case. The skin, scleræ and mucous membranes were a deep yellow color. The tissues about the *eyes* were swollen and discolored, no other edema. There were a few small hemorrhages in the *skin* over the right flank. The cranial cavity was normal except for a yellow color of the dura. The *heart* and *lungs* were normal, except for moderate patchy congestion of the cut surfaces of the *lungs*, and a small area of subendocardial hemorrhage 1 cm. in diameter in the left ventricle.

Adhesions were found in the *abdominal cavity*, between the omentum, the transverse colon and the parietal peritoneum, between the diaphragm and the edge of the liver, and in the cul-de-sac about the pelvic organs. The *stomach* was moderately distended with fluid containing black flecks and partly digested food. The gastric mucosa was atrophic and covered with a thick layer of mucus. The pyloric ring was slightly thickened with an inside circumference of 3.5 cm. The duodenum was drawn to the right by adhesions to the under surface of the liver in the area of the removed gall bladder. *The descending portion of the duodenum was completely surrounded by a ring of pancreatic tissue, which rather markedly constricted the lumen*, so that it would not admit the tip of the small finger (Fig. 1). The

inside circumference of the duodenum above the ring was 6 cm., the diameter of the constriction was 1.2 cm., and the circumference below the ring was 5 cm. The common bile duct was patent. There was a moderate amount of bloody fluid in the duodenum with the mucosa edematous and congested. The remainder of the small bowel contained a large amount of bloody fluid and gas. The large bowel was heavy with tarry stool and distended with gas. A large redundant cecum extended 7 cm. below the ileocecal valve. The appendix had been removed.

The *pancreas* was normal, except for the annular portion which seemingly arose from the posterior portion of the head and encircled the duodenum to the right with slightly decreasing size to fuse with the uncinate portion anteriorly (Fig. 1). Posteriorly the ring measured 15 mm. in width and 9 mm. in thickness. Anteriorly it tapered to 10 mm. in width and 5 mm. in thickness. There was a branching duct in the annular portion, which increased in caliber as it circled around the duodenum from front to back (Fig. 2). It was joined by a similar-sized duct arising in the dorsal portion

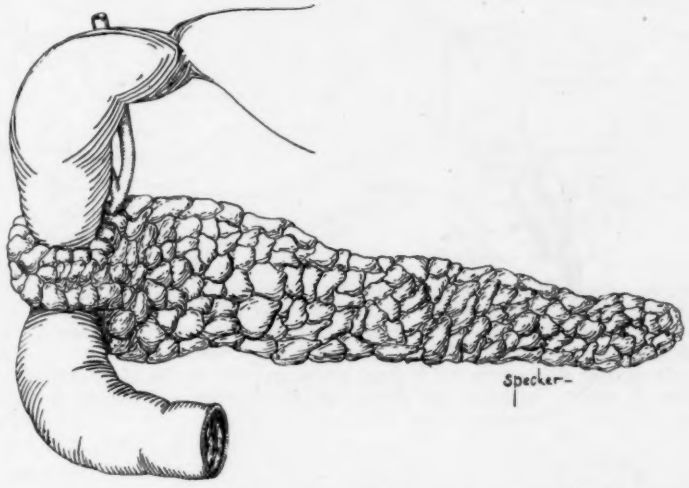

FIG. 1.—Author's case of annular pancreas, causing constriction of the second portion of the duodenum with slight dilatation of the first portion.

of the head of the pancreas. This united duct of Wirsung measured 5 mm. in circumference and emptied at the duodenal papilla 3 cm. below the lower posterior border of the ring, together with the normal common duct. The branched ducts from the remainder of the pancreas emptied into the duodenum at the lesser ampulla, 1 cm. below the ring, through the accessory pancreatic duct, which also measured 5 mm. in circumference. No connecting duct between the main and the accessory pancreatic ducts was demonstrable.

The *liver* measured 27 by 21 by 9 cm., and was markedly yellow. The cut surface showed yellow parenchyma with the centers of the lobules standing out as minute red dots. The *kidneys* were swollen, the capsules stripped readily, surfaces smooth; cut surfaces opaque with the glomeruli visible as fine translucent bodies. The *ureters* and *bladder* were normal, except for slight mucosal congestion. The *spleen*, *adrenals* and *aorta* were normal. The right *ovary* and both *tubes* had been removed. The left ovary was drawn over to the body of the *uterus* by dense adhesions. The uterus was normal other than a few small cysts in the cervix.

Essential Microscopic Findings. Stomach. The mucosa was markedly atrophic with the outer portion of the glands devoid of epithelium, areas of necrosis, heavy layers of mucus, and no lymphoid tissue. The submucosa and muscular layers were normal. *Liver:* Fatty infiltration, degeneration, and necrosis of the liver cells were marked about the centers of the lobules, with only small remnants of normal cells peripherally. The central areas of necrosis were filled with delicate vascular fibrous tissue in which were fusiform cells containing brown granular pigment and a moderate number of lymphocytes. *Kidney:* There were a few small cortical scars, marked cloudy swelling of the tubular epithelium, with small areas of necrosis and a large amount of granular material in the tubules and glomerular spaces. *Pancreas:* Sections from the head, the tail and the annular portion were all normal pancreatic tissue.

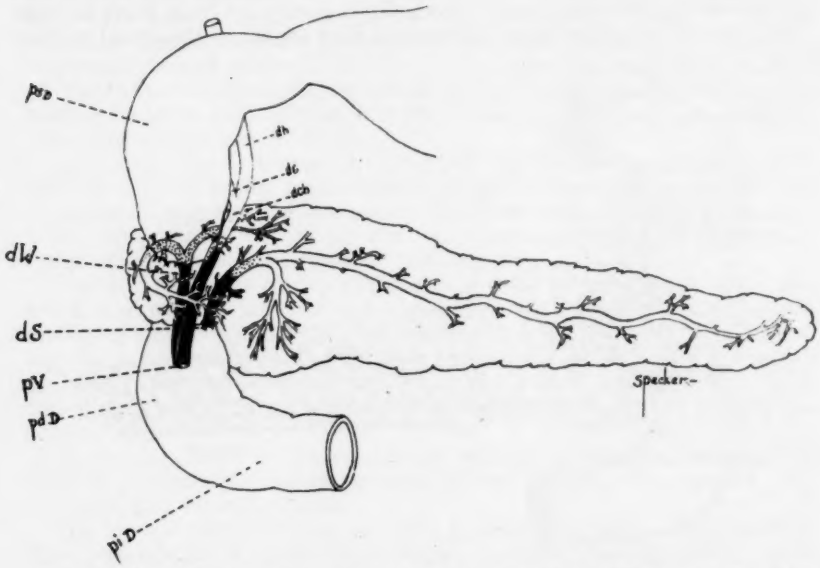

FIG. 2.—Diagram of the arrangement of the ducts in the author's case of annular pancreas. *psD*, pars superior duodeni; *dW*, ductus Wirsungi; *dS*, ductus Santorini; *pV*, papilla of Vater; *pdD*, pars descendens duodeni; *piD*, pars inferior duodeni; *dh*, ductus hepaticus; *dc*, ductus cysticus; *dch*, ductus choledochus.

Anatomical Diagnosis: 1, Chronic alcoholism; 2, chronic gastritis; 3, cirrhosis, early subacute; 4, jaundice, toxic; 5, fatty liver; 6, hemorrhage, gastrointestinal tract; 7, congenital malformation of pancreas (annular pancreas); 8, operations, cholecystectomy, salpingectomy, oöphorectomy, appendectomy, healed; 9, chronic cervicitis; 10, chronic, adhesive, local peritonitis.

Discussion of Literature. Embryologists[1] state that the human pancreas arises in the embryo as two entirely distinct entodermal outgrowths, known as the dorsal and ventral anlages respectively. The dorsal anlage grows out from the dorsal wall of the intestinal tube, slightly above the level of the common bile duct. The ventral anlage grows in the inferior angle formed by the hepatic diverticulum, and the intestine, and may be more or less bi-lobed. As the

ventral and dorsal anlages elongate, rotation of the stomach and elongation of the bile duct cause the ventral anlage to approach the dorsal, and ultimately unite with it as diagrammatically shown in Figs. 3 and 4.

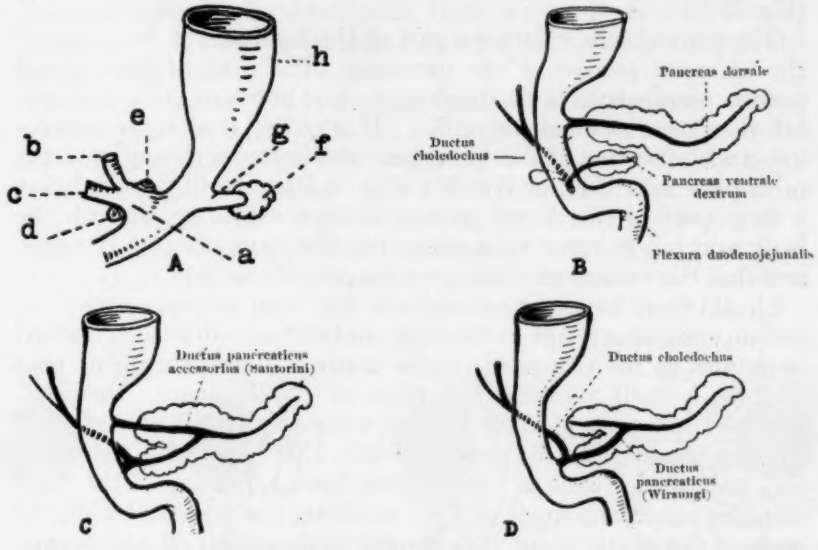

FIG. 3.—Diagrammatic development of the pancreas. *A*, the early pancreatic buds: *a*, common bile duct; *b*, hepatic duct; *c*, cystic duct; *d*, right, and *e*, left ventral pancreatic anlages; *f*, dorsal pancreas and its duct, *g*; *h*, stomach. (After Piersol.[2]) *B*, *C*, *D*, the normal migration of the ventral to fuse with the dorsal anlage, the establishment of the pancreatic duct of Wirsung which empties through the duodenal papilla in common with the ductus choledochus. (After Corning in Braus.[3])

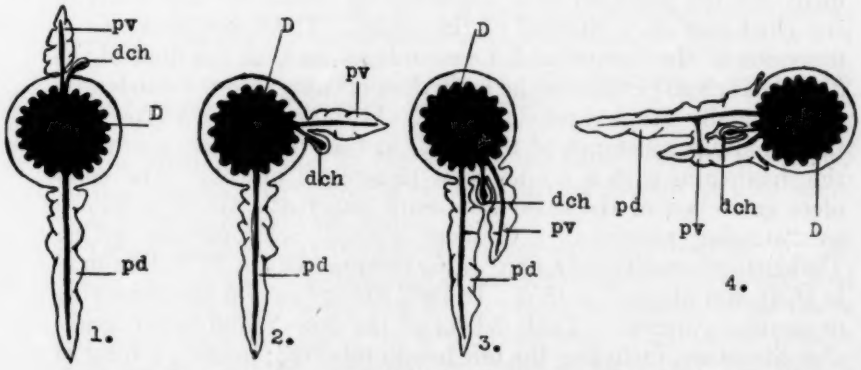

FIG. 4.—Diagrammatic representation of the normal migration of the ventral pancreatic anlage, *pv*, to fuse with the dorsal anlage, *pd*, enclosing the ductus choledochus, *dch*, between them. The anastomosis of the ducts is shown in 4, *D*, duodenum. (After Lecco.[4])

The dorsal anlage is larger than the ventral, and grows across the body toward the left, until it reaches the spleen. It gives rise to

the body, the tail and the ventral portion of the head of the adult gland. Its duct opens into the duodenum above the orifice of the common bile duct, and usually anastomoses with the ventral duct. Its outlet persists as the accessory pancreatic duct of Santorini (Fig. 3, *C*).

The ventral anlage forms a part of the head and more or less of the uncinate process of the pancreas. The duct of the ventral portion usually ends in the duodenum, close beside or in the common bile duct near its duodenal orifice. This ventral duct by an anastomosis with the duct of the dorsal pancreas becomes the outlet of the main pancreatic duct of Wirsung (Fig. 3, *D*). It will be noted that a large part of the dorsal pancreatic duct extending through the body and tail becomes incorporated in this main duct of Wirsung, and that the ventral pancreas supplies only the outlet.

Should there be any interference in the usual sequence of events, certain anomalies result. Opie[5] and Simkins[6] have described marked variations in the pancreatic ducts, hence it is not surprising that the gland itself presents anomalies of development. Simpson[7] collected 150 cases of aberrant pancreatic tissue, and offered Warthin's explanation as the most plausible. "It is probable that acessory pancreatic tissue is formed from lateral budding of the rudimentary pancreatic ducts as they penetrate the intestinal wall, the mass of pancreatic tissue thus formed being snared off and carried by the longitudinal growth of the intestine either upward or downward." "Pancreas minus" describes a condition in which a portion of the pancreas is separated from the remainder by a more marked depression than usual. "Pancreas divisum" is the partial division of the body of the gland by pressure from the vessels during development but the parts are still connected by means of their ducts to the chief excretory channel of the organ. There are instances of nonunion of the ventral and dorsal anlages, so that the duct of the dorsal pancreas persists as the main duct opening into the duodenum at a normally situated papilla minor. At times there is a growth of the glandular substance of the head, so that it partially surrounds the duodenum with a semicircular pancreatic process. The complete encircling of the duodenum with pancreatic tissue is known as "annular pancreas." Gruber[8] quoted Schirmer[9] as giving Tiedemann[10] credit for first recording this anomaly in 1818, Bécourt[11] in 1830, and Moyse[12] in 1852. In 1862 Ecker[13] gave it the name ring or annular pancreas. Table 1 lists all the cases found in the available literature, including the one herein reported; making a total of 40 cases.

Tieken[14] suggested two possible theories to explain the annular pancreas: (1) "If the ventral and dorsal diverticulums did not unite as they normally do, but each developed independently, there would be pancreatic tissue on either side of the intestine, and as growth proceeded, the bowel would soon be completely

surrounded by glandular tissue." (2) "In the semiannular type, the condition might be due to an overdevelopment of the head, which sends out processes, partially surrounding the bowel; if this hypertrophy should continue until the processes meet on opposite sides of the duodenum, there would be a true annular pancreas." Symington's[15] case suggested this second theory, and Brines[16] favored it.

Baldwin[17] stated "It is a significant fact that the specimens of annular pancreas which have been dissected show a duct traversing the ring and joining dorsally with the main pancreatic duct, not emptying into the accessory duct. This seems to indicate that this ring of tissue is either a persistence of the left half of the ventral anlage, or an excessive growth from the right half of the same anlage. If it is this latter case, the excessive growth has taken place ventral

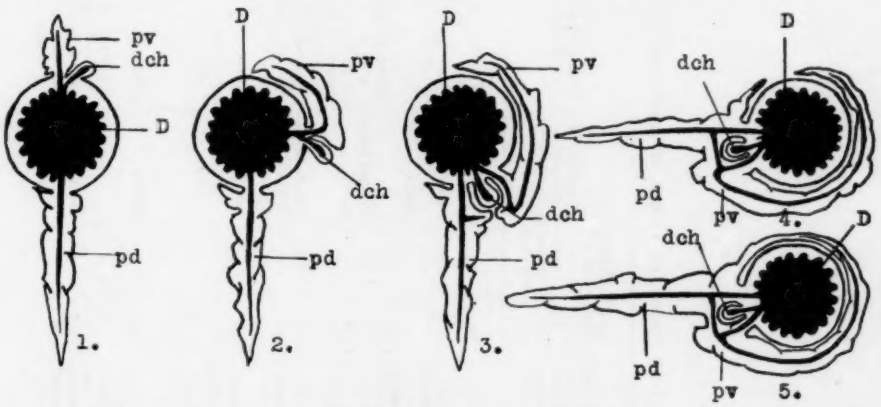

FIG. 5.—Diagrammatic representation of the mode of development of the annular pancreas. The free end of the ventral pancreatic anlage, *pv*, becomes fixed so that during its subsequent migration, with the rotation of the duodenum, *D*, toward the dorsal anlage, *pd*, it is drawn out. With the fusion as shown in 5 it comes to surround the duodenum. (After Lecco.)

to the duodenum, and to the left, at the time that the remainder of the same half was growing or being carried dorsally to ultimately fuse with the head of the gland."

Lecco[4] believes that the annular pancreas differs from the normal gland only in the ring-forming portion which arises from the dorsal portion of the head of the pancreas. The arrangements of the ducts are comparable to those of the normal pancreas. He does not believe that the ring can be explained by simple hypertrophy, but that it owes its origin to an anomaly of the ventral pancreatic anlage, the tip of which becomes adherent to the duodenal wall, and in the normal migration it is stretched to form the ring. Fig. 5 as suggested by Lecco graphically explains his theory. Cords[18] and Smetana[19] also adhere to the embryonic theory, that the ring portion arises from the ventral anlage.

TABLE 1.—COMPILATION OF REPORTED CASES OF ANNULAR PANCREAS.

Reporter.	Date.	Age.	Sex.	Signs and symptoms.	Location (portion of duodenum.)	Constriction of duodenum. +	Dilatation of duodenum above the ring.	Condition of stomach.	Course of duct in the ring.	Operation.	Other congenital defects.
1. Tiedemann[10]	1818	....	..	.....	....	....	....	.....	.....	.....	.....
2. Bécourt[11]	1830	....	..	.....	....	....	....	.....	.....	.....	.....
3. Moyse[12]	1852	....	..	.....	....	....	....	.....	.....	.....	.....
4. Ecker[13]	1862	"Young man"	M.	.....	Second	+	+	.....	o. i. m. d.*	.....	Bicuspid valve defect.
5. Auberg[24]	1866	....	M.	.....	Fourth	+	....	.....	.....	.....	.....
6. Symington[15]	1885	"Adult"	M.	.....	Second	+	+	.....	"Nothing unusal"	.....	.....
7. Genersich[25]	1890	37	M.	.....	Second	+	+	Dil. and hyper.	o. i. m. d.	.....	.....
8. Thacher[21]	1893	....	..	.....	....	+	....	.....	.....	.....	Accessory pancreas.
9. Sandras[26]	1897	70	M.	.....	Second	+	+	.....	.....	.....	.....
10. Summa[27]	1900	....	..	.....	....	....	....	.....	.....	.....	.....
11. Tieken[14]	1901	34	M.	None	Second	+	++	Hyper. sl. dil.	"Normal"		
12. Vidal[22]	1905	3 days	..	Vom., visible peristalsis	Second	+	....	Normal	.....	Post. gastroenterostomy; recov.	Duod. atresia.
13. Santos[28]	1906	26	F.	Epig. pain, vom. food reten.	Second	+	....	Dil., 2 ulcers	.....	Gastroenterostomy; death	.....
14. Ott[29]	1909	....	..	.....	....	....	....	.....	.....	.....	.....
15. Lerat[30]	1910	46	F.	Gast. upsets (24 years); liquid food 3 mos., right epigastric resist., belching, const.	Second	++	+	.....	.....	Gastroenterostomy	.....
16. Baldwin[17]	1910	....	..	.....	Second	+	±	Normal	o. i. m. d.	.....	.....
17. Lecco[4]	1910	....	..	.....	Second	+	+	.....	"	.....	.....
18. Lecco	1910	....	..	.....	Second	+	+	.....	"	.....	.....
19. Cords[18]	1911	"Senile"	M.	.....	Second	+	....	.....	"	.....	Duod. divertic.
20. Benedetti[31]	1920	"Soldier"	M.	Ao. intest. obstruc.	Second	++	+	Dilated	.....	.....	.....
21. Gruber[32]	1920	58	M.	.....	Second	+	+	.....	"Normal"	.....	.....

22.	Bell[20]	1922	4 mos.	M.	None	Second	+	....	.....	o. i. duod. ab. and post. to ampulla; (m.d.o. with bile duct into ampulla)	.....	Intervent. septum defect; patent for. ovale and duct. art.; Meckel's divertic.; umbil. and ing. hernia; horiz. and vert. process besides ring of panc.
23.	Priesel[45]	1923	70	M.	.....	....	....	....	.....	.....	.....	.....
24.	Anderson[24]	1923	....	M.	.....	Second	+	+	Dilated	Formed m. d.	.....	.....
25.	Kurozawa[25]	1923	1½	M.	.....	....	....	....	.....	.....	.....	.....
26.	Kurozawa	1923	64	M.	.....	....	....	....	.....	.....	.....	.....
27.	Susukida[26]	1924	3½	F.	.....	....	....	....	.....	.....	.....	.....
28.	Shibata[27]	1924	....	M.	.....	....	....	....	.....	.....	.....	.....
29.	Key[22]	1924	"Old"	F.	.....	Second	+	+	.....	o. i. m. d.	.....	Curv. of spine; duod. divertic.
30.	Sugawara-Shibata[28]	1925	Fetus 8 mos.	M.	.....	....	++	....	.....	.....	.....	Anal atresia.
31.	Hennes[39]	1928	5 days	M.	Bloody stools	Second	++	+	Dilated	.....	.....	.....
32.	Thür[40]	1928	66	M.	None	Second	+	+	.....	Emptied chiefly into accessory duct; small portion i. m. d.	.....	.....
33.	Smetana[19]	1928	1 mo.	M.	.....	Second	++	+	Normal	o. i. m. d.	.....	Anal atresia; club foot; cleft palate; undescended testes; aplasia l. kidney and ureter.
34.	Smetana	1928	70	M.	None	Second	+	+	.....	"	.....	.....
35.	Smetana	1928	74	M.	Vom., const., abd. pain	Second	+	+	Dilated	"	Gastroenterostomy; death	.....
36.	Howard[41]	1930	46	F.	Ac. pain in R. U. Q., vom.	Second	+	++	Normal	o. i. m. d.?	Release of panc. ring; recov.	.....
37.	Brines[16]	1930	35	M.	Coffee-ground vom., R. U. Q. rigidity, tender., const., collapse	Second	+	+	Dilated	o. i. m. d.	Explor. laparot. death, ac. hem. panc.	.....
38.	Ehlers[42]	1930	25	F.	None	Second	+	++	.....	"	.....	.....
39.	Brines[43]	1931	44	M.	Epig. pain, belching, vom.	Second	+	+	Dilated, ulcer	.....	Gastroenterostomy; death	.....
40.	McNaught	1932	37	F.	Indig. for years; ac. epig. pain, tarry stools, mod. rigid. R. U. Q., coffee-ground vom. recent	Second	+	±	Dilated, fluid	"	None	Redundant cecum.

* o. i. m. d. = opened into main duct.

The specimen in Bell's[20] case resembled the pancreas of a cat, in that it had a horizontal and a vertical process, and in addition an annular pancreas. The position of the pancreatic ducts in this specimen indicated that the annular part developed from the dorsal anlage, inasmuch as its duct opened into the lesser ampulla, while the ducts from the "split pancreas" opened into the ampulla of Vater along with the common bile duct. There were so many congenital malformations associated with this case that it must not be considered on the same basis as most of the other cases. The cases reported by Ecker,[13] Thacher,[21] Vidal,[22] Cords,[18] Keyl,[23] and Smetana[19] were associated with some degree of congenital malformation. Keyl suggested that the congenital curvature of the spine in his case may have played a part in compressing the duodenum and displacing the anlages.

Discussion of Cases. The clinical significance of annular pancreas is readily seen in Table 1, where practically all carefully described cases showed more or less constriction of the second portion of the duodenum, with varying degrees of dilatation of the proximal portion of the small bowel, pylorus and stomach. Specific statements as to the patient's abdominal signs and symptoms were given in only 15 of the 40 cases. In 9 of the 15 (60 per cent) signs and symptoms of high intestinal obstruction were present in varying degrees, hence annular pancreas must be recognized as a clinical entity and considered in all cases presenting such symptoms. In other cases the anomaly was an accidental finding at autopsy or in the dissecting room. Several cases were not reported in detail but were described merely as anatomical curiosities. The fact that the ages ranged from fetal life to 74 years indicates that it is possible to live the normal span of life with this anomaly without serious consequence. The danger lies in the fact that conditions causing swelling of the pancreatic ring, such as hemorrhage, pancreatitis, tumor, hypertrophy, etc. may rapidly bring on acute intestinal obstruction.

Seven of the 40 cases of annular pancreas were operated upon due to upper abdominal signs and symptoms. Gastroenterostomy was the chosen procedure in 5. Howard[41] recommended duodenojejunostomy after observing the stormy convalescence following the severing of the pancreatic ring in his case with the accompanying cyst and sinus formation.

Fifty-seven and a half per cent of the reported cases of annular pancreas were found in males, 17.5 per cent in females and in 25 per cent the sex was not given. This probably has no significance since there are usually more male than female cadavers in the dissecting rooms and among the cases autopsied. In the 9 cases with definite upper abdominal signs and symptoms, 4 were males, 4 females and in 1 the sex was not mentioned.

In 88 per cent of the cases in which the arrangement of the ducts was clearly stated, the duct of the ring portion was a part of the

main pancreatic duct of Wirsung. This is a strong indication that the annular portion is a developmental anomaly of the ventral pancreatic anlage.

In the author's case, gastric and duodenal irritation due to alcoholism which caused edema and congestion of the mucosa thus increasing the constriction of the duodenum at the pancreatic ring, combined with cirrhosis and adhesions, was probably responsible for some of the signs and symptoms.

Summary. 1. An additional case of annular pancreas is reported along with a compilation of other reported cases, bringing the total number up to 40. These few cases probably reflect less than the true incidence of this condition; but it is hoped that by directing attention to these the annular pancreas may receive its proper place as a clinical and anatomical entity.

2. The bulk of the evidence indicates that annular pancreas is a developmental anomaly of the ventral pancreatic anlage. It usually causes constriction of the second portion of the duodenum.

3. It has produced signs and symptoms of high intestinal obstruction in a few cases, hence must be recognized as a clinical entity and considered in all such cases.

4. Gastro-enterostomy has been the most favored surgical procedure for annular pancreas.

5. This anomaly has been reported in individuals ranging from fetal life to 74 years of age.

6. Of the reported cases 57.5 per cent have been in males, 17.5 per cent in females and in 25 per cent the sex was not given. This probably has no significance.

7. Twenty per cent of the cases were associated with other congenital anomalies.

8. In the author's case, annular pancreas, chronic alcoholism, gastritis, cirrhosis, and adhesions probably combined to cause the clinical signs and symptoms.

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SOME LIMITATIONS IN THE TREATMENT OF CHRONIC PEPTIC ULCER WITH GASTRIC MUCIN.*

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In a preliminary report published about 1 year ago, Fogelson[1] introduced the use of gastric mucin in the treatment of peptic ulcer. At this time he reported 12 patients who obtained complete relief

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from symptoms within 3 days and remained well for periods of 2 to 5 months. This communication was followed several months later by an account[2] of equally striking results obtained in a series of 66 out of 68 patients with chronic peptic ulcer, 15 of whom had previously resorted to surgical intervention. Some of these patients remained asymptomatic for as long as 20 months after the inception of mucin therapy. Kim and Ivy[3] reported the prevention of ulcer formation in 17 dogs with biliary fistula by feeding 15 gm. of mucin twice daily. Later, Rivers, Vanzant and Essex,[4] in a study of more than 40 cases treated with mucin reported "very encouraging results . . . in some instances," but in others "no advantage over the present approved method" could be observed. More recently, Fogelson[5] reported only 7 failures out of a series of 113 patients, of which 56 had been refractory to all other forms of treatment. Atkinson,[6,7] in a report of 85 cases, including 11 post-operative recurrences, found that his patients became asymptomatic within the average period of 2.2 days. Brown,[8] in a preliminary report of his study of 37 intractable cases, 21 of which were hospitalized, found that the average patient became asymptomatic within 8 days and in no instance did a recurrence manifest itself. He encountered but 1 failure in this group. His patients were observed for periods as long as 1 year. Coincident with the subjective improvement, Fogelson, Atkinson and Brown noted a considerable gain in weight and a distinct improvement in the hematologic and roentgenologic picture.

Following Fogelson's first favorable report[1] we undertook a careful study of its clinical value. In this report we wish to relate our experiences and point out the advantages and disadvantages over the present orthodox method.

At the outset we determined the effect of mucin and its fractions upon the gastric acidity and compared it with that of a milk and cream mixture. While our results are to be reported in detail elsewhere* a few remarks concerning our findings seem appropriate: Of 13 experiments on 8 patients with peptic ulcer, the achlorhydria following ½ oz. of gastric mucin persisted for from 15 to 90 minutes, not exceeding 30 minutes in the majority, although the total average was 40. The neutralizing capacity of the peptone-phosphate fraction (ash) which constitutes 40 per cent of commercial mucin, plays no inconsiderable rôle in the antacid property of mucin. The mild secretagogue effect originally noted by Fogelson[1] in his Pavlov pouch dogs, and confirmed by Ivy and Kim,[9] was corroborated by our studies on patients, for of 21 experiments with mucin and its derivatives, a mild or moderate hyperstimulation was observed in 14 (66 per cent). Rivers, Vanzant and Essex[9,10] reported a marked secretagogue effect in some of their patients and, from supplementary

* Accepted by the Journal of Laboratory and Clinical Medicine.

studies, concluded that it was due to a histamin substance present in certain batches of mucin. A 3 oz. mixture of milk and cream (equal parts) compared favorably with the average achlorhydric response to ½ oz. of gastric mucin but was devoid of secretagogue effect. Although the "modus operandi" of mucin in ulcer therapy does not yet appear to be clear, the latter findings point more to its action as a demulcent than to its acid-combining power, a conclusion in accord with the views more recently expressed by Fogelson[5] and his collaborators.[6,7,8]

Clinical Procedure. In each patient a careful detailed anamnesis was procured, especial emphasis being laid upon the response to previous forms of treatment and the duration of remissions. The diagnosis was made by the usual clinical and roentgenologic methods. Only cases of ulcer uncomplicated by other disease were chosen. Gastric mucin was given to 28 patients, of whom 24 had a duodenal ulcer, 1 had a duodenal and a gastric ulcer, 1 a gastric ulcer, 1 a pyloroplasty and 1 a pyloroplasty and gastrojejunostomy. Eight were hospitalized and at rest in bed; the others were ambulatory, being seen in the gastro-intestinal clinic of the Michael Reese Hospital and in private practice. Many of them had in the past received thorough present-day medical supervision and nearly all had derived more or less satisfactory though temporary relief. Many had ulcer symptoms for several years and, having followed various régimes without permanent relief, welcomed any new form of treatment which would ward off an operation. Three additional patients treated with mucin elsewhere are included in our series.

The method of its administration was that at first suggested by Fogelson[1] in his preliminary report (1 oz. 3 times daily with the meals and 20 to 30 grains in capsules every hour between meals) and later modified after hearing some minor changes advocated by him in a personal communication (½ oz. 5 times daily between meals and 20 grains in capsules every 2 hours). As further suggested,[11] belladonna was given to those who had a pylorospasm. If the capsules of mucin produced epigastric or substernal distress, they were omitted and the powder alone used in increased amounts, thereby compensating for the deficit. When diarrhea occurred, indicating an inability to "digest" such quantities of mucin (Fogelson[11]), the amount was diminished to the point of individual tolerance and, wherever possible, subsequently increased. In no case had the patient been taking more than 40 grains of alkalies daily before mucin was given.

The diet consisted of milk and cream, cereals, poached or soft boiled eggs, custards, gelatine puddings, cocoa, ice cream, toast and butter, seedless jams and jelly, fruit juices and puréed fruits and vegetables. Boiled or broiled meat was not added until 3 weeks after the patient became symptom-free.

Roentgen ray studies were made every 3 months in order to detect any changes in the ulcer defect.

Results. The results of our experience may be divided into five groups: 1, those refusing to continue mucin; 2, unimproved; 3, improvement and relapse while under treatment; 4, generally improved; 5, miscellaneous.

1. Patients Refusing to Continue Mucin. Table 1 shows that 6 patients discontinued the use of mucin within a period of 1 to 7 days. In 2, intense nausea precluded its administration beyond 1 day and 1 week respectively. In 4, nausea accompanied by vomiting appeared. In 1 of these repeated vomiting followed the first and only dose, while in another retention vomiting occurred every evening, the vomitus containing many undigested capsules together with large quantities of mucin. On the seventh day he developed constant intense boring pain indicative of a penetrating lesion. In 3 the predominating symptoms of pain or heartburn or both became intensified and in 2 of these nausea and vomiting were associated, profuse vomiting 6 hours later giving complete relief in 1. In all of these patients substitution of alkalies for mucin effected immediate relief from the untoward symptoms and they became totally asymptomatic in a few days. (Wherever alkalies were given it was generally in the form of calcium carbonate, or occasionally sodium bicarbonate, 10 grains 3 times daily.)

Table 1.—Patients Refusing to Continue Treatment.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Reason for stopping mucin.
S. L.	42	M	10 yrs.	1 wk.	Increase of pain; relief with Pfunder's* tablets.
E. D.	46	M	20 yrs.	1 day	Severe pyrosis shortly after mucin; slight relief with soda; complete relief after profuse vomiting 6 hrs. later; nausea.
B. M.	27	M	2 yrs.	2 days	Intense nausea; vomiting.
H. L.	24	F	5 yrs.	1 dose	Nausea; recurrent vomiting; could not tolerate taste or smell.
M. S.	26	M	4 yrs.	7 days	Nausea; retention vomiting; increased pain; relief with diet and alkalies.
M. K.	42	F	6 yrs.	2 days	Intense nausea.

* The chemists for the American Medical Association reported "that Pfunder's Stomach Tablets apparently contained bismuth subnitrate, 30.5 per cent; magnesium oxide, 22.8 per cent; baking soda, 24.4 per cent."

2. Unimproved. Symptoms of these 8 patients (Table 2) had been present for periods ranging between 2 and 13 years. One had previously had an excision of the ulcer with a pyloroplasty and 1 had both a duodenal and a gastric ulcer. Mucin was given for periods of 3 weeks to 3 months, the majority receiving it for 3 to 6 weeks. Three patients manifested a slight diminution in the

intensity and duration of symptoms for 7, 8 and 18 days respectively, only to be followed by a relapse without any further improvement. One of these noted an increased number of stools during the first week.

TABLE 2.—UNIMPROVED.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
S. A.	39	M	5 yrs.	3 wks.	Improved first week; 2 to 3 b. ms. daily; recurrence second week; discontinued after 3 weeks.
J. M.	53	F	"Years"	25 days	Slightly improved first 18 days; then recurrence.
S. D.	34	F	7 yrs.	27 days	Improved first few days; then recurrence.
D. W.	48	M	12 yrs.	4 wks.	Pain and pyrosis worse; heaviness, bloating, vomiting, lost weight; improved with alkalies.
J. S.	41	M	2–3 yrs.	6 wks.	Recurrent pain and pyrosis; longest period of relief—10 days.
B. L.	43	M	7 yrs.	5 wks.	Nausea and vomiting at first, then relief 4 days and recurrence; relief 4 mos. with Pfunder's tablets; recurrence; mucin again; pain and pyrosis worse; Pfunder's tablets 4 days later—relief.
M. B.	34	M	10 yrs.	6 wks.	Epigastric heaviness; frequent vomiting, 6th wk.; increased pain; "better without mucin."
I. B.	48	M	13 yrs.	3 mos.	Epigastric distress worse 1st 4 days; vomiting 7th day (never before); improved next 11 days; then relapse; no improvement after 3 mos.

One patient (D. W.), who was being treated successfully for a gastric ulcer by the use of diet and alkalies, but who still showed a definite though smaller Haudek's niche, was placed on the same diet without alkalies. Three weeks later, his symptoms having recurred, the efficacy of mucin was tested over a period of 4 weeks. The pain and heartburn became worse, heaviness and bloating appeared, he vomited once and in 4 weeks lost $3\frac{1}{2}$ pounds. Maximum doses of belladonna were also tried. Restoration to alkalies (by request of patient) produced immediate and progressive improvement.

In another (B. L.), nausea and vomiting were present during the first 2 days and although mucin was taken for 5 weeks, relief from his ulcer symptoms was noted for only 4 days. He finally resorted to alkalies, derived complete relief in a few days, felt well and ate all types of food for 4 months before he had another recurrence. Mucin was again tried but the symptoms became more severe and more constant. Four days later he voluntarily discontinued mucin and reported immediate relief from alkalies. In the other 2 patients (M. B. and I. B.) mucin apparently intensified the existing symptoms and induced vomiting. One of these discontinued mucin at the end of 6 weeks because of recent repeated vomiting and reported an amelioration of symptoms after the resumption of alkalies.

J. S. complained of bloating after each mucin feeding and noted

alternating relief and recurrence, the longest free interval being 10 days. Mucin was discontinued 6 weeks later on his own accord.

3. Improvement and Relapse While Taking Mucin. We observed 6 patients who, first manifesting improvement, subsequently developed recurrent symptoms while taking mucin. As shown in Table 3 symptoms had been present periodically for as long as 3 to 16 years. One had a pyloroplasty and a later gastrojejunostomy with evidence of a recurrent ulcer. Mucin was given to this group for 3.5 to 8.5 months, improvement beginning immediately in 4 cases and not until the lapse of 5 to 17 days respectively in 2 others. Improvement continued uninterruptedly for 12 days to 5.5 months and was followed by recrudescences lasting as long as 3 months.

Table 3.—Improvement and Relapse While Taking Mucin.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
J. W.	38	M	5 yrs.	5 mos.	Nausea and heaviness 3 wks.; anorexia; occasional vomiting; improvement began 5th day; alternating relapse and improvement; worry! improvement with belladonna.
J. L.	41	M	5 yrs.	3½ mos.	Immediate relief of pain for 7 wks.; epigastric fullness as before; finally ate everything; pain recurred; diet restricted again; no relief.
H. H.	29	M	8 yrs.	7 mos.	Relief after 17 days; improved 14 wks.; anorexia; stopped mucin (nausea, cramps, diarrhea); recurrence; mucin again, 3 mos.; no relief; colon symptoms returned; operation: 2 duodenal ulcers.
M. R.	40	M	3–4 yrs.	3½ mos.	Immediate moderate improvement for 4 wks.; recurrence, nausea, vomiting, cramps, diarrhea, lost weight; improved with diet and alkalies.
H. R.	43	M	10 yrs.	8½ mos.	Immediate improvement; gained weight; flatulence; 5½ mos. later pain recurred; dosage increased; gradual improvement; 3 mos. later occasional pain.
A. T.	45	M	16 yrs.	4 mos.	Immediate progressive improvement 12 days; then alternating improvement and relapse for 2 mos.; no further improvement; constipation relieved.

When mucin was substituted for alkalies, the diet remaining the same, J. L. (pyloroplasty and gastrojejunostomy) noted immediate relief of pain and subsequently was able to eat a larger variety of foods, although the heaviness and bloating continued to be present after each feeding. A recurrence set in abruptly 7 weeks later with no further response despite dietary restrictions. Remissions of the same or longer duration had been observed previously while on alkalies.

In 2 patients (H. H., M. R.), abdominal cramps, borborygmi and diarrhea appeared 1 to 2 months after mucin was started. In 1 of

these (H. H.), reducing the dosage (to 70 gm.) improved these symptoms, but the constantly recurring nausea constrained him to discontinue mucin. Concomitantly the colon symptoms disappeared, only to reappear when mucin therapy was again attempted. No improvement in the ulcer symptoms was apparent 3 months after renewing the mucin. At operation, soon afterward, 2 active kissing duodenal ulcers were found. In the other patient the diarrhea disappeared following temporary reduction of mucin, but abdominal cramps continued. Later nausea and vomiting appeared during or after each mucin feeding, necessitating supplementary feedings to insure the proper intake (90 gm.). After his relapse had persisted 2.5 months the substitution of alkalies effected an immediate progressive improvement in the ulcer symptoms and a prompt subsidence of the untoward symptoms.

N. O. improved immediately and, except for the flatulence which disappeared as the dosage was reduced to 75 gm. daily, remained well 5.5 months when his symptoms returned. By increasing the mucin to 100 gm. daily he slowly improved but still complained of occasional pain 3 months later. One patient (A. T.) reported gradual improvement for 12 days, followed by short periods of relapse and improvement, finally becoming refractory to further mucin therapy. J. W. manifested a response somewhat similar to the latter, although marked improvement was observed only after maximum doses of belladonna were given. It is noteworthy that most of his recurrences followed periods of great financial stress and strain.

In all of these patients the blood and stool examinations were normal throughout and the weight remained constant. In no instance were we able to detect any improvement in the Roentgen ray appearance of the duodenal bulb. Further, it is pertinent to remark that during the period of observation the dosage of mucin was unaltered except in the cases cited.

4. Generally Improved. Seven patients may be relegated to the domain of "generally improved." They had complained of recurrent distress for 10 months to 15 years. To date, as seen from Table 4, 6 have received mucin for 3 to 5 months. One patient became asymptomatic immediately but was not seen after his discharge from the hospital 1 week later.

Immediate improvement was noted in 4 others. Of these, 1 was symptom-free after the 1st day; another after the 4th day, the former manifesting no response to diet and alkalies during the previous 5 weeks, whereas the latter, during an earlier recurrence, had responded to diet alone in 1 week. Of the remaining 2 who improved immediately the relief was more gradual and while recurrences, usually mild and of short duration, occurred in both, the response was distinctly better than that following alkali therapy during previous recurrences.

TABLE 4.—GENERALLY IMPROVED.

Name.	Age.	Sex.	Duration of symptoms.	Mucin period.	Comments on results.
B. S.	42	M	"Years"	4 mos.	Diarrhea, cramps, belching, increased pyrosis for 4 wks.; then improvement of all symptoms on 75 gm. daily with belladonna.
C. D.	34	M	6 yrs.	5 mos.	Gradual improvement; nausea 1st wk.; relapse 5th wk. for 5 days; feels well except occasional pain; gained 5 pounds.
I. D.	24	M	2 yrs.	5 mos.	Immediately improved; 3 recurrences lasting 3–15 days; takes 65 gm. daily; gained 6 pounds.
S. R.	47	M	7 yrs.	3½ mos.	Diarrhea (6 b. ms. daily) and flatulence first few days—disappeared on less mucin (65 gm.); no pain after 4 days; heartburn gradually improving; gained 4 pounds.
I. C.	35	M	2 yrs.	3 mos.	Nausea 1st wk.; anorexia; immediate relief of pain.
M. S.	23	M	10 mos.	4 mos.	Anorexia and increased pyrosis 1st wk.; then progressive improvement; asymptomatic 19th day; diarrhea, lower abdominal pain; no ulcer pain.
R. M.	30	M	15 yrs.	1 wk.	Immediate improvement; did not return.

One patient began to improve on the 7th day and was asymptomatic on the 19th day. Another did not show any improvement until the end of 4 weeks, when belladonna in maximum doses was given. In both, however, the symptoms were intensified at first. The former patient had been on a diet alone for the preceding 2 weeks and the latter on a diet with small daily doses of alkalies for 3 weeks, both without any relief.

Nausea was present for 1 week in 2. Diarrhea, lower abdominal cramps and flatulence appeared in 3, necessitating a constantly reduced dosage (to 65–75 gm. daily) in 2 and making mucin prohibitive in the third (M. S.), although total relief from his ulcer symptoms obtained while taking the mucin.

The weight remained constant in 3, whereas 3 others gained from 2 to 6 pounds. Blood and stool examinations were normal throughout. In no instance was there a disappearance of the duodenal defect, as demonstrated by repeated roentgenologic studies.

5. MISCELLANEOUS. In this group we have included 3 patients who had been treated with mucin elsewhere, but who consulted us relative to a different form of therapy. One discontinued mucin because of the intense nausea which it provoked. Another reported 2 recurrences, the last recurrence persisting for 3.5 months despite large amounts of mucin in conjunction with belladonna. He improved immediately and became asymptomatic within 2 weeks after being placed on the usual milk and cream and alkali régime. The third patient received mucin for 6 months with only slight relief for 2 months, followed by a relapse and no further response. He

had previously visited the Mayo Clinic, where surgery was recommended. Our Roentgen ray studies disclosed a typical clover-leaf deformity. An emergency operation performed a short time later revealed a large perforated duodenal ulcer.

Because we can not justifiably assign his response to any of the aforementioned groups we are including the case of D. F. in this category. Aside from occasional heartburn, his only symptoms were repeated hemorrhages occurring as long as 1.5 years apart. In the interim he was able to eat all forms of food with impunity. We had hoped, therefore, to prevent further hemorrhages by mucin therapy. To date he has taken mucin for 5 months without any apparent hemorrhages. Seven weeks after starting mucin, however, he developed intense epigastric pain, heartburn, belching and repeated vomiting, all of which subsided in 2 weeks. His Roentgen ray films still show a definite duodenal defect.

TABLE 5.—MISCELLANEOUS.

Name.	Age.	Sex.	Duration of symptoms.	Mucin. period.	Comments on results.
D. F.	41	M	1½ yrs.	5 mos.	Asymptomatic at outset except for hemorrhages; pain, pyrosis, vomiting, belching 7 wks. after starting mucin, lasted 2 wks.; no recurrent hemorrhages.
M. B.*	42	M	"Years"	6 mos.	Slight improvement 2 mos.; relapse; no further improvement; perforated shortly after.
S. S.*	50	M	5 yrs.	1 wk.	Nausea; discontinued mucin.
W. B.*	34	M	6 yrs.	1 yr.	Relief in 1 wk.; 2 recurrences later while taking mucin; relief by alkalies and diet after persistent symptoms for 3½ mos.

* Treated with mucin (90 to 100 gm. daily) elsewhere.

TABLE 6.—UNTOWARD SYMPTOMS DURING MUCIN THERAPY.

	Refused to continue.	Unimproved.	Improved and relapse.	Improved.	Miscellaneous.	Total.
Symptoms intensified	1	1	..	2	..	4
Nausea	1	..	1	2	2	6
Nausea and vomiting	2	1	2	..	..	5
Nausea, vomiting and pain	2	3	..	..	1	6
Anorexia	..	..	1	2	..	3
Flatulence	..	3	3	3	1	10
Diarrhea	..	1	..	1	..	2
Diarrhea and cramps	..	..	2	2	..	4

Untoward Symptoms. We have found no report containing a record of the untoward symptoms which may confront the physician. Accordingly we have reviewed our cases from this aspect. Table 6 shows the frequency with which we encountered an intensification

of the prevailing symptoms, anorexia, nausea, vomiting, cramps, diarrhea and flatulence. That these symptoms are of no little importance is evidenced by the fact that by virtue of their presence some patients were compelled to discontinue mucin entirely, even though definite relief had been achieved; others were unwilling to give it an adequate trial and still others had to reduce the dosage, a factor which may have inhibited more striking results in some. In many, epigastric distress was noted for some time after the capsules were swallowed.

Comment. The natural cycle of events experienced by individuals with chronic peptic ulcer, its disposition toward spontaneous remissions lasting for longer or shorter periods of time during which any type of food may be consumed with absolute impunity, recurrences as well as remissions which are antedated by and related to changes in the psyche, as well as other recognized factors must obviously make it extremely difficult to evaluate properly the advantages purported to be derived from any medicament designed for the relief of ulcer symptoms. Further, that a diet consisting of puréed fruits and vegetables and other well comminuted foods, such as Fogelson[1,2] recommends in the beginning of mucin therapy, will by itself in many cases be conducive to a remission, irrespective of the number of previous recurrences, is a frequent observation. Consequently, we simultaneously observed as controls a group of 15 patients with peptic ulcer of many years' duration, whom we treated by a similar diet, adding alkalies and belladonna wherever indicated. Our results to date have been almost uniformly satisfactory, some becoming asymptomatic immediately. None of them developed alkalosis or other untoward symptoms. Again, in our mucin series we observed several refractory cases which responded immediately to the substitution of alkalies.

It is noteworthy nevertheless that partial or complete symptomatic relief was achieved with mucin in 7 patients who failed to respond to other forms of therapy. Such results indicate that gastric mucin may have a place in the treatment of peptic ulcer, notwithstanding the shortcomings previously discussed as untoward symptoms, although prolonged observation under carefully controlled conditions is essential to the formulation of any definite conclusion. One may not anticipate many cures, however, because of the frequent operative and necropsy findings of larger or smaller penetrations into the pancreas, the intrinsic and extrinsic scar formations, their resultant influence upon the normal physiology of the stomach and especially the duodenum and the impossibility of normal anatomic restitution. At the present writing, then, we should advocate its use in cases refractory to other forms of treatment and as a step toward the evasion of a surgical procedure. In view of the many available proprietary forms of mucin it is important that a preparation free from histamin substances,[4,10] such

as the one we used, be administered. It is hoped that certain refinements in the manufacture of gastric mucin will ultimately eliminate the untoward symptoms herein recorded.

Conclusions. 1. Gastric mucin probably acts not through its acid-combining power but by virtue of its demulcent effect.

2. Experience with 30 mucin treated patients, as compared with 15 ulcer cases receiving other forms of treatment, shows that some will not continue its use because of the disagreeable taste and certain untoward symptoms. In others, prolonged administration effects no relief, whereas other forms of treatment are successful. In still others, relief is temporary and followed by a relapse. In the remainder relief occurs with mucin when other forms of therapy fail.

3. Further refinements in its manufacture may widen its scope of usefulness in the treatment of peptic ulcer.

NOTE.—We wish to acknowledge our indebtedness to Dr. David Klein of the Wilson Laboratories, who so kindly supplied us with the mucin. We are also grateful for the coöperation extended by the Misses S. Elkin, N. Taylor and D. Elliott of the dietetic department of the Michael Reese Hospital.

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REVIEWS.

MAN AND MEDICINE. By DR. HENRY E. SIGERIST, Professor at the University of Leipzig. Introduction by DR. WILLIAM H. WELCH, Professor of the History of Medicine, The Johns Hopkins University. Translated by Margaret Galt Boise. Pp. 340. New York: W. W. Norton & Co., Inc., 1932. Price, $4.00.

IN his foreword, Professor Welch says "Designed primarily to present in broad outlines a picture of modern medicine, with its historical and cultural background to students entering upon the study of their profession, the interesting character of this presentation, the artistic and orderly arrangement of the subject matter, the clear and flowing literary style, well preserved, in Margaret Boise's translation, the broad principles enunciated and especially the historical treatment makes the work scarcely less welcome to other cultivated readers, both medical and lay."

There is no doubt but that this statement is a happy one, and it reiterates the purpose and intention of the author who says that "This book is intended primarily to acquaint young people who have chosen to enter medicine with the nature of their studies and their future profession. . . . It would please me should the book stir the interest of physicians as well."

We have carefully read the book and enjoyed it immensely, but while doing so, could not help meditating upon the primary purpose as expressed by both author and introducer, and wondering whether its appeal to the graduate who will understand what it is all about and be familiar with the terms and the facts, will not be immensely greater than to the beginner who will no doubt be as astonished at the amazing breadth of the subject he hopes to learn as bewildered by its terminology.

It is quite true that no physician will find the terminology other than simple and commonplace; a well-educated layman will understand it, but a youth just out of college must possess considerable perseverance as well as great interest in medicine if he ever finishes it.

Occasional amusing mistakes in translation occur: one such on page 217 is the confusion of the words "hybrid" and "bastard" that leads to the astounding statement in the last paragraph that "*all humans are bastards.*" But this in no manner diminishes the excellence of the work, for no one incapable of realizing the error will ever read it.

As we have enjoyed and profited by the book ourselves, we are glad to recommend it to others, especially, however, to graduates of medicine.

J. McF.

PSYCHOPATHOLOGY OF FORCED MOVEMENTS AND THE OCULOGYRIC CRISES OF LETHARGIC ENCEPHALITIS, MONOGRAPH SERIES NO. 55. By SMITH ELY JELLIFFE, M.D., PH.D., of New York, N. Y. Pp. 219; 26 illustrations. New York: Nervous and Mental Disease Publishing Company, 1932. Price, $4.00.

INCLUDED in this thesis is an abstract of the more than 200 cases of lethargic encephalitis, reported up to 1931, in which there had occurred the oculogyric crisis. In addition, the author analyzes the 4 cases of patients seen by him in consultation.

The crisis is not an early manifestation of the disease and nearly always it is confined to the Parkinsonian type. The eye spasms may be tonic, clonic or spasms of convergence. The crises may last from a few minutes to one or more days and may occur several times a day or may be a month apart. Certain psychological manifestations usually accompany it: "2. The thought movement is slowed. 3. The emotional state is mostly one of conscious anxious compulsion. 4. Involvement of consciousness (vigilance) varies from slight to marked degrees of involvement." In the final chapter, Psychopathology, is given the Freudian interpretation of these interesting phenomena, supplemented by the author's personal views.

This monograph is a welcome contribution to the literature of lethargic encephalitis. The bibliography is voluminous, mostly foreign, and there is a fair index. N. Y.

THE EXPECTANT MOTHER'S HANDBOOK. By FREDERICK C. IRVING, A.B., M.D., Professor of Obstetrics, Harvard Medical School, etc. Pp. 203; 26 illustrations. New York: Houghton Mifflin Company, 1932. Price, $1.75.

THIS is an excellent manual on pregnancy for the average woman. The important topics as hygiene, diet, minor complications and danger signals serve as an excellent standard for discussion by the physician of the proper course of life of his maternity cases. The chapter on anesthesia in labor might serve very well to offset some of the hysterical outbursts by lay writers in the past few years. Some of the material in the final chapter on evolution and heredity seems too technical for the average woman. The book is rather sparsely illustrated. A widespread distribution of this book would do much to promote an intelligent interest in maternity problems among the laity. P. W.

CANCER: CIVILIZATION: DEGENERATION. By JOHN COPE. Pp. 293; 55 illustrations. London: H. K. Lewis & Co., Ltd., 1932. Price, 15/- net.

IF the student hopes to find in this book advanced scientific information about *cancer*, he will meet with disappointment, for the author, though a practitioner of medicine, is a philosopher and sociologist, and not a biologist, pathologist or scientific oncologist. His idea is "to go back to the time before the first cancer research laboratory was built and continue the wide methods of investigation then in vogue." This enables him to avoid technicalities and "direct his words to the medical profession in general, and to the educated members of the general public."

But the method involves him in errors, leads to dogmatic statements upon insufficient data, and to conclude his book with philosophical speculations of questionable validity. The work more or less abounds with the familiar but false statement, used, for instance, by Willy Meyer and James Tobey, that "cancer has become one of the most curable of all diseases." Can ignorance account for such a statement or is there an international propaganda in this direction? Whatever the experience of those experts who treat large numbers of "cancer cases" with "great success," it must be remembered that they only meet with that success in carefully selected cases of appropriate types of tumors. With such facts in mind is it not wicked to place before a lay reader, intelligent as he may be, the statement that "cancer has become one of the most curable of all diseases"? It has not! Few cases are cured, and the incidence and death rate continually rise! But the reader soon finds that the only cases that are so "curable"

are "very early cases." Hence a variation of the original propaganda to "come early to get cured." But Cope goes further; the real time to come is before there is a cancer. Use every possible means of preventing it.

The author believes his vital message to be that cancer is caused by *Degeneration.* It, in turn, is the result of disease, inactivity or inadequacy of those organs in which it most frequently develops. This argument is pursued systematically. Degeneration of the jaw, resulting in defective teeth, results from civilization and the change of foods from the tough and gritty bones and nuts ground up by the teeth of our savage ancestors, to the soft "paps" and "porridges" eaten by the spoon-fed youth of the present day. The improved quality of the foods leave no "roughage" for the stomach and intestines to work upon and they also soon "degenerate" with resulting gastro-enteroptosis, appendicitis, ulcers and cancers. Lack of use is the chief cause of the degeneration that results in the cancer. It is interesting to see this argument applied to the organ of sex, and the overwhelming prevalence of cancer of the uterus and breast referred to disuse and consequent degeneration of those organs! A lengthy digression upon sex and its problems, and a somewhat tedious philosophic speculation upon social, moral, political and esthetic decadence somewhat along the lines made familiar by Lothrop Stoddart and Robert Briffault, winds up with the philosophical and sophistical conclusion that "To prevent cancer, therefore, our first object must be to exercise those organs which in the circumstances of our civilization are now being insufficiently used and thus to cause their invigoration and rejuvenation."

To one crushed under the wheel of misfortune, who has just been told that he is the victim of cancer, it is small comfort to learn that it might have been prevented if some thousands of years ago his stone-age ancestors could have been persuaded to continue to eat the same coarse foods, and to breed large families as rapidly as possible. Nor does it appeal strongly to the writer of this review to look hopefully to the future elimination of the disease by having our descendants of some thousands of years hence, revert to the same supposedly more beneficial manners and customs of savagery.

J. McF.

DISEASES OF THE CORONARY ARTERIES (MYOCARDITIS). By DON C. SUTTON, M.S., M.D., Associate Professor of Medicine, Northwestern University, etc., and HAROLD LUETH, PH.D., M.D., Formerly Instructor Physiology, Northwestern University, Chicago. Pp. 164; 42 illustrations, 3 colored plates. St. Louis: The C. V. Mosby Company, 1932. Price, $5.00.

THIS book is the result of the senior author's desire to answer various perplexing questions that have been asked him on the basis of his compiled experiences plus an unbiased review of the literature. Accepting the thesis of Huchard, that the cardiac symptoms of chronic cardiovascular disease are the product of arteriosclerosis of the heart, which is synonymous with chronic myocarditis, he includes "(Myocarditis)" in the title—a point of view which we hope is being increasingly abandoned today. Angina pectoris, dogmatically set down as the result of arteriosclerosis of the coronary arteries in the Introduction, is considered on page 28 *et seq.* from the various customary points of view, the authors apparently concluding that it may be caused by any one of several conditions producing an insufficient blood supply. Chapter II, Physical Examination of the Heart, is concerned chiefly with electrocardiography; Chapter III, Anatomy, entirely with Gross' description of the blood supply. Chapter IV, Pathology, having listed 3 possible causes of interstitial changes in the myocardium (acute

arteritis, toxic or bacterial interstitial proliferation and primary muscle degeneration), discusses *i. a.* Buerger's disease, gumma, infarct, pericarditis. A certain lack of orderly arrangement adds to difficulties of comprehension; thus the summary at the end of Chapter V is found to summarize only part of the chapter; other chapters have no summary; Fig. 42 (an experimentally produced aneurysm in a dog), seems to have landed on p. 151 purely by accident. A list of 213 references should prove useful, though it is by no means exhaustive or even up to date. Thus while the book undoubtedly has its uses, it is disappointingly far from being the help that one might look for. E. K.

ENGLISH-SPEAKING STUDENTS OF MEDICINE AT THE UNIVERSITY OF LEYDEN. By R. W. INNES SMITH, M.D. (EDIN.), With Foreword by JOHN D. COMRIE, M.D., F.R.C.P. (EDIN.), Lecturer on the History of Medicine at the University of Edinburgh. Pp. 258; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price, 16/– net.

To American medicos the University of Leyden should always have an especial interest on account of Boerhaave's great influence, chiefly exerted through the University of Edinburgh and English medicine, on 18th century medicine in this country. This book contains well over 2000 names of English, Scotch, Welsh and Irish students at Leyden, and yet the Reviewer was able to find only a few Americans among them (Cp. "John Adams, the Virginia Americanus, 1794, Med."). This confirms the statement made to the reviewer a few years ago that he was the first American to work in the Boerhaave laboratory at Leyden for more than a century.

Going beyond Peacock's publication in 1882 of an "Index to the English Speaking Students who have Graduated at Leyden University," the present volume not only lists all those who have attended the University but follows (except in the case of the most famous) their subsequent career in a concise manner that conveys a wealth of information in a small space, often derived from almost inaccessible sources. This painstaking work should be not only invaluable to students of medical history but also a stimulus to its readers to visit this charming center of learning. The influence of Leyden was so great for over a century that it was the most sought after resort of those seeking the best in medical education. To-day it not only produces and harbors eminent scholars but preserves to a marked degree the charming atmosphere of its former eminence. The old University building with its Senate Chamber and its adjoining waiting room for the candidates about to be examined ("Hic sudavit sed non frustra"), Boerhaave's "Hortus" and the adjacent shop of the famous Elzevirs are well worth a visit, as those who attended the recent Congress of Medical History there can testify. E. K.

CALIFORNIA'S MEDICAL STORY. By HENRY HARRIS, M.D., Associate Clinical Professor of Medicine, University of California; Chief of Medical Department, San Francisco Polyclinic. With an Introduction by CHARLES SINGER, M.D., D. LITT., University of London, London, England. Pp. 421; illustrated. San Francisco: J. W. Stacy, Inc., and Springfield, Illinois: Charles C Thomas, 1932. Price, $7.00.

THE growing list of state medical histories being published in this country, if the additions and standards continue at the present rate, bids fair not only to provide much instructive "local" entertainment, but also to ensure a corpus of American medical history data that would hardly otherwise be

accumulated. This, the latest of the series, has certain novel features that especially commend it to the general (in addition to the local) reader. As Charles Singer points out in the Introduction, "For the study of medical history, California presents quite exceptional advantages. The geographical isolation of its population makes a true local study more valid than would be the case for most states. The earlier records have been better and more lovingly preserved in California than in any other civilization that has developed so recently and so rapidly. The presence of first-class library facilities is unique for so youthful an aggregate. The very rapid evolution of Californian civilization has carried with it a no less rapid evolution of medicine from the primitive and magical to the highly scientific, though no less human, discipline which is enabling the medical schools of the State to provide as well equipped medical men as are to be found anywhere in the world." A good balance has been maintained between readability and documentation, illumined by gleams of humor, which occasionally are at the State's expense. The local taboo of climate is touched upon with humorous satire. The volume has been beautifully prepared by the Grabhorn Press with unusually attractive type and paper. Even the difficult subject matter of the illustrations has been successfully handled. The extensive bibliography and careful indices further add to a splendid production. E. K.

THE HOUSE THAT FREUD BUILT. By JOSEPH JASTROW, PH.D., LL.D. Pp. 293. New York: Greenberg, 1932.

THE method of psychoanalysis can hardly have failed to arouse the curiosity if not the active concern of specialists, general practitioners and thoughtful laymen who are impressed by the increasing strain that the complexities and tension of modern life have put on the "psyche" and by the evidence of its increasing failure to stand up under this strain. Attempts to evaluate the psychoanalytic method, however, are made so difficult and the overemphasis of sex has been so repugnant to the average man that the psychoanalytic method today remains about as much *sub judice* as at any time since its discovery 50 years ago. From its very nature the truth of its premises can never be tested, as could the bacterial theory of infectious disease, for instance, and the therapeutic test is notably difficult and fallacious. Holding to the middle course, the author discusses in nontechnical language the pros and cons of this important topic, giving due weight to its achievements and properly discounting its exaggerations. This evaluation then by an unbiased, skillful writer on psychological topics should prove valuable to many. E. K.

ANESTHESIA. By W. STANLEY SYKES, M.A., M.B. (CANTAB.), D.P.H. (LEEDS), M.R.C.S., Anesthetist to the General Infirmary at Leeds, etc. With a section on Local Anæsthesia by P. J. MOIR, M.C., M.B. (GLASGOW), F.R.C.S. (ENG.), Hon. Assistant Surgeon, General Infirmary at Leeds, etc. Pp. 128; 6 illustrations. New York: W. W. Norton & Co., Inc., 1932. Price, $2.00.

SYKES has crowded into one small book much practical experience concerning inhalation anesthesia. In Part I on "General Principles" he outlines clearly first the essential rules to be followed in the administration of an anesthetic, and then details the psychologic aspect of anesthesia, and the treatment of the various complications that may arise. In Part II on "Methods" he devotes chapters to each of the usual inhalation anesthetics

used in England. Ethyl chlorid, chloroform and the less commonly used anesthetic mixtures are fully discussed, whereas ethylene, avertin and rectal anesthesia are dismissed with a paragraph or two. Part III on Local and Regional Anesthesia is little more than a brief description of the method. The complications and their remedies, so clearly detailed in the first part of the book are conspicuous by their absence in Part III. The book is excellent as a practical handbook for beginners in general anesthesia.

L. F.

THE HEART RATE. By ERNST P. BOAS, M.D., Associate Physician, Mt. Sinai Hospital, New York City and ERNST F. GOLDSCHMIDT, PH.D., Research Fellow (1930–1931), Department of Surgery in the Yale University School of Medicine. Pp. 166; 68 illustrations of figures and charts. Springfield, Illinois: Charles C Thomas, 1932. Price, $3.50.

BOAS and GOLDSCHMIDT studied the diurnal and nocturnal variations in heart rate by means of the cardiotachometer, an instrument for the continuous recording of heart beats. Observations were carried out in 103 normal adults over periods of from 12 to 24 hours, showing the variations in heart rate accompanying sleep, exercise, food-taking and various other episodes of daily life. Studies of 27 young boys undertaking exhausting exercise, and of 77 patients undergoing anesthesia and operation are reported. The last chapter consists of observations on "The Heart Rate in Disease." A number of small groups of patients were studied: Hyperthyroidism (10), Neurocirculatory Asthenia (12), Progressive Muscular Dystrophy (7), Poliomyelitis (7), Valvular Disease (9), Active Rheumatic Myocarditis (?), Congestive Heart Failure (?), Arthritis Deformans (?), Auricular Fibrillation (?), and Heart Block (?). (The Question marks indicate that the number of patients is not stated.)

The observations reported in this book are carefully made and of considerable interest. The authors have occasionally been tempted to be a little uncritical in their discussion of the implications of some of their observations.

F. W.

BOOKS RECEIVED.

NEW BOOKS.

Men Against Death. By PAUL DEKRUIF. Pp. 363; illustrated. New York: Harcourt, Brace & Co., 1932. Price, $3.50.

Physical Chemistry for Students of Biology and Medicine. By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 182; 26 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $2.75.

Oral Spirochetes and Related Organisms in Fuso-spirochetal Disease. By DAVID T. SMITH, A.B., M.D., Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C. Pp. 243; 53 illustrations. Baltimore: The Williams & Wilkins Company, 1932. Price, $4.50.

A Manual of Embryology. By J. ERNEST FRAZER, F.R.C.S. (ENG.), Professor of Anatomy in the University of London; Lecturer at the Medical School of St. Mary's Hospital, etc. Pp. 486; 282 illustrations. New York: William Wood & Co., 1932. Price, $8.00.

A Guide to Human Parasitology. By D. B. BLACKLOCK, M.D. (EDIN.), D.P.H. (LOND.), D.T.M. (LIVER.), Professor of Parasitology, Liverpool School of Tropical Medicine, the University of Liverpool, etc., and T. SOUTHWELL, D.Sc., PH.D., A.R.C.Sc., F.Z.S., F.R.S.E., Lecturer in Helminthology, School of Tropical Medicine, Liverpool, etc. Pp. 271; 122 illustrations and 2 colored plates. New York: William Wood & Co., 1932. Price, $4.00.

Anleitung zur Frühzeitigen Erkennung der Krebskrankheit. By various contributors. Pp. 134. Leipzig: S. Hirzel, 1932. Price, Rm. 3.–.

Varicose Veins and Haemorrhoids. By V. MEISEN, M.D., Former Chief Surgeon to the Policlinic, Sundby Hospital, Copenhagen. With a Preface by AUG. KROGH, PH.D. Pp. 149; 25 illustrations and 8 colored plates. Copenhagen: Levin & Munksgaard, 1932, and London: Oxford University Press, 1932. (No price given.)

Non-tropical Sprue. By TH. E. HESS THAYSEN, M.D., Senior Physician to the St. Elisabeth's Hospital, Copenhagen. Pp. 258; 39 illustrations. Copenhagen: Levin & Munksgaard, 1932, and London: Oxford University Press, 1932. (No price given.)

Radiologic Maxims. By HAROLD SWANBERG, B.Sc., M.D., F.A.C.P., Editor, the Radiological Review; Radiologist, Saint Mary's Hospital and Blessing Hospital, Quincy, Ill., etc. With a Foreword by HENRY SCHMITZ, A.M., M.D., LL.D., F.A.C.R., F.A.C.S., Professor of Gynecology and Head of the Department, Loyola University School of Medicine, etc. Pp. 127. Quincy, Ill.: Radiological Review Publishing Company, 1932. Price, $1.50.

Experimental Analysis of Development. By BERNARD DÜRKEN, Professor in the University of Breslau. Translated by H. G. and A. M. NEWTH. Pp. 288; 120 illustrations. New York: W. W. Norton & Co., Inc., 1932. Price, $4.75.

Habits. Their Making and Unmaking. By KNIGHT DUNLAP, Professor of Experimental Psychology in the Johns Hopkins University. Pp. 326. New York: Liveright, Inc., 1932. Price, $3.00.

Streptococci in Relation to Man in Health and Disease. By ANNA W. WILLIAMS, M.D., First Assistant Director, Bureau of Laboratories, Department of Health, City of New York. Pp. 260; 7 plates, 1 figure and 19 tables. Baltimore: The Williams & Wilkins Company, 1932. Price, $5.00.

Poliomyelitis. A Survey Made Possible by a Grant from the International Committee for the Study of Infantile Paralysis. Organized by JEREMIAH MILBANK. Pp. 562; 24 plates (1 in color), 82 tables and 19 charts. Baltimore: The Williams & Wilkins Company, 1932. Price, $6.00.

The Surgical Clinics of North America, Vol. 12, No. 6 (Philadelphia Number, December, 1932). Pp. 280; 110 illustrations. Philadelphia: W. B. Saunders Company, 1932.

The Medical Clinics of North America, Vol. 16, No. 3 (University of California Number, November, 1932). Pp. 195; 31 illustrations. Philadelphia: W. B. Saunders Company, 1932.

Growth. By the late JAMES LORRAIN SMITH, M.D., LL.D., D.Sc., F.R.S., Professor of Pathology, University of Edinburgh. Edited by J. S. HALDANE, C.H., M.D., F.R.S. Pp. 131; 1 illustration. Edinburgh: Oliver & Boyd, 1932. Price, 6/– net.

The 1932 Year Book of Radiology. Diagnosis. Edited by CHARLES A. WATERS, M.D., Associate in Roentgenology, Johns Hopkins University; Assistant Visiting Roentgenologist, Johns Hopkins Hospital. *Therapeutics.* Edited by IRA I. KAPLAN, B.Sc., M.D., Director, Division of Cancer, Department of Hospitals, City of New York, etc. Pp. 750; 498 illustrations. Chicago: The Year Book Publishers, Inc., 1932. Price, $6.00.

Modern Alchemy. By WILLIAM ALBERT NOYES, University of Illinois, and W. ALBERT NOYES, JR., Brown University. Pp. 207; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1932. Price, $3.00.

The Diagnosis and Treatment of Postural Defects. By WINTHROP MORGAN PHELPS, B.S., M.D., M.A., F.A.C.S., Professor of Orthopedic Surgery, Yale University, etc., and ROBERT J. H. KIPHUTH, Assistant Professor of Physical Education, Yale University, etc. Pp. 180; 107 illustrations, 14 tables. Springfield, Ill.: Charles C Thomas, 1932. Price, $4.00.

NEW EDITIONS.

The Early Diagnosis of the Acute Abdomen. By ZACHARY COPE, B.A., M.D., M.S. (LOND.), F.R.C.S. (ENG.), Surgeon to St. Mary's Hospital, Paddington; Senior Surgeon to the Bolingbroke Hospital, Wandsworth Common, etc. Pp. 248; 30 illustrations. Sixth edition. New York: Oxford University Press, 1932. Price, $3.25.

Outline of Preventive Medicine. Prepared Under the Auspices of The Committee on Public Health Relations, New York Academy of Medicine. By 24 Contributors. Editorial Committee: FREDERIC E. SONDERN, CHARLES GORDON HEYD, and E. H. L. CORWIN. Pp. 462. Second edition, revised and enlarged. New York: Paul B. Hoeber, Inc., 1932. Price, $5.00.

"Following the suggestions made by the reviewer of the book, three new chapters have been added and additional material included in many of the other chapters" (24). (From the Editorial Committee's Introduction.)

A Laboratory Manual of Physiological Chemistry. By D. WRIGHT WILSON, Benjamin Rush Professor of Physiological Chemistry, University of Pennsylvania. Pp. 284. Second edition, thoroughly revised. Baltimore: The Williams & Wilkins Company, 1932. Price, $2.50.

"It might be emphasized to students using this manual that it is not intended as a reference book. The experiments have been selected to furnish experience and information in the various branches of physiological chemistry. Certain quantitative methods have been chosen from among a large number available on account of their didactic value and the relatively simple outfit of laboratory apparatus required for their execution." (From the Author's Preface.)

A Text-book of Pathology. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, Johns Hopkins University, Baltimore. Pp. 1212; 652 illustrations. Fifth edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1932. Price, $10.00.

An Introduction to Dermatology. By NORMAN WALKER, KT., M.D., LL.D., F.R.C.P., Consulting Physician for Diseases of the Skin, The Royal Infirmary, Edinburgh. Assisted by G. H. PERCIVAL, M.D., PH.D., F.R.C.P., Assistant Physician. Pp. 382; 100 plates (82 in color) and 92 text illustrations. Ninth edition. New York: William Wood & Co., 1932. Price, $7.00.

This edition differs from the preceding largely because the therapeutic teachings have been so thoroughly revised—a change made necessary by the many newer methods which have developed in the dermatological field in the past 8 years. Twenty-eight new illustrations and plates have been added, together with three dermatoses which have more recently secured places as dermatologic entities.

PROGRESS
OF
MEDICAL SCIENCE

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UNDER THE CHARGE OF

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Tobacco Sensitiveness in Thromboangiitis Obliterans.—One of the earliest suggestions as to the etiology of thromboangiitis obliterans was that it in some way depended upon the overuse of tobacco. Various other hypotheses have been advanced, such as a specific infection, an endocrine imbalance or a toxic factor being responsible, tobacco being the most frequent toxic agent. Probably there would be a greater belief in the importance of this plant in the etiology of the disorder if it could be shown that all individuals who are so diseased use tobacco, but in many instances of thromboangiitis obliterans the patients have not used tobacco of any kind. The great majority, however, have been heavy smokers. HARKAVY, HEBALD and SILBERT (*Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 104) have recognized the importance of this weed plant in the etiology of thromboangiitis obliterans, and Silbert, particularly, has studied the incidence of the disease in smokers and nonsmokers. He has observed no typical incidence of the disease in men who did not smoke and he likewise has seen clinical improvement in the disease when the use of tobacco was stopped. The question has been further studied by investigating the specific hypersensitiveness to tobacco. Sixty-eight cases of the disease were studied, and 122 controls who were heavy smokers. A goodly number of the latter were Russian Jews. Extracts of tobacco were prepared in several ways and five different extracts were tested on every case of thromboangiitis obliterans and every control by the usual methods of testing skin sensitivity. Eighty-three per cent of the cases of thromboangiitis obliterans reacted to one or another of the tobacco extracts with varying degrees of intensity. Of the controls about 10 per cent gave a reaction, none of which was marked. Among the controls were 15 patients who had circulatory disturbances of the lower extremities, arteriosclerotic in character, all of whom were tobacco negative. Among 15 persons suffering from hay fever, all reacted positively to tobacco, whereas only 2 of the 68 patients with thromboangiitis obliterans reacted to ragweed. Fifteen of these patients, however, reacted to other antigens, but in all of them tobacco was the dominant one. From these studies the authors attempt to draw no definite conclusions other

than that a large percentage of the patients suffering from thromboangiitis obliterans are allergic and that this allergy is characterized by hypersensitiveness to tobacco.

The Blood Picture in Exophthalmic Goiter and Its Changes Resulting from Iodin and Operation. A Study by Means of the Supravital Technique.—Ordinary methods that have been used routinely for the past quarter of a century in counting the blood are being supplemented more and more by more highly specialized studies than those used in the past. The introduction of a comparatively simple technique of supravital staining of blood examination has made this possible. An example of these types of studies is seen in the paper by HERTZ and LERMAN (*J. Clin. Invest.*, 1932, **11**, 1179), who studied the blood of patients suffering from exophthalmic goiter. They found that the most characteristic and marked alteration from the normal blood picture in patients with exophthalmic goiter consisted in a relative and absolute increase in the number of monocytes, the figure averaging 14.1 as contrasted with the normal average of 5.7. The percentage of lymphocytes was also increased, although the absolute number was normal. Discrepancies of the blood reports of the past have arisen probably from misclassifying monocytes as lymphocytes. The monocytes tend to increase with an increase in the basal metabolic rate, whereas the lymphocytes have a downward tendency as the metabolism rises. After the administration of iodin there occurs a reduction both in the total number and the percentage of polymorphonuclears and a decrease in the lymphocytes. This reduction in the monocytes is proportional to the reduction in the absolute metabolic rate. Operation on the thyroid is followed by an increase in the total number of leukocytes as a result of an increase of polymorphonuclears and monocytes, of which only the percentage of monocytes has changed significantly. After operation, in the final changes in the blood picture it is noted that there is a lowering of the metabolic rate that is proportionately greater than the change in the blood picture. The authors correlate Aschoff's ideas concerning the monocyte of the circulating blood being a part of the reticuloendothelial metabolic apparatus with their own results, hinting that activation of this system occurs in hyperthyroidism and that iodin depression is linked with a depression of the reticuloendothelial system.

SURGERY

UNDER THE CHARGE OF

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Methods for Administering Fluids.—In the last issue we reviewed briefly the fluid and salt requirements of surgical patients. The next step is to determine the methods by which the materials required may

be supplied. This is especially true in those patients in which the fluid and salt loss is great. There can be no doubt but that the oral method is by far the best if there is not contraindication to the administration of fluids by mouth. With the aid of a Jutte tube large amounts of fluid containing salts and nutritive material can be administered. Unfortunately in the abdominal cases of an obstructive or suppurative character the oral method cannot be used. The subcutaneous method is useful, but even when used as suggested by BARTLETT (*Ann. Surg.*, 1921, **73**, 161) with the addition of novocain to the solution it is painful. It cannot, as a rule, be used over a period of many days and free movements of the patient are definitely restricted. The rectal or colonic method has the disadvantage that over long periods the rectum is apt to become intolerant. Furthermore, when large amounts of fluid are necessary this method is not adequate in itself. FLEMING (*J. Am. Med. Assn.*, 1931, **97**, 6) has shown that large amounts of fluid in the colon may initiate the spread of an abdominal infection by stimulating peristalsis, a condition which we seek above all to avoid in abdominal suppuration. Increasing evidence published during the past 2 years indicates that little, if any, glucose is absorbed from the rectum or colon. Indeed, MCNEALLY and WILLEMS (*Surg., Gynec. and Obst.*, 1929, **49**, 794; *Arch. Surg.*, 1931, **22**, 649) found that when glucose was added to the fluid placed in the colon the absorption of water was retarded. The work of the above authors and that of PRESSMAN (AM. J. MED. SCI., 1930, **179**, 520), EBELING (*Ibid.*, 1932, **183**, 876) and SCOTT and ZWEIGHAFT (*Arch. Int. Med.*, 1932, **49**, 221) are in agreement that little, if any, glucose is absorbed by this route. Certain of these studies were made in man while others were made in experimental animals. EBELING (AM. J. MED. SCI., 1932, **183**, 876) found that only in the markedly hypoglycemic animal did the absorption of glucose from the colon approach that from the ileum. PERUSSE (*Surg., Gynec. and Obst.*, 1932, **54**, 770), on the other hand, found that a 1 per cent solution of glucose was absorbed to a greater degree than was a 5 per cent solution. However, the total amount absorbed even when the 1 per cent concentration is used is so small as to be of very little therapeutic value. Most of those who have studied the subject agree that tap water and normal saline are rapidly absorbed from the rectum and colon. The intravenous method has the advantage of permitting fluid to be placed directly in the blood stream. The fluid may be introduced at a predetermined rate so that the amount of fluid, salt and glucose introduced can be accurately estimated. The paper of MATAS (*Ann. Surg.*, 1924, **79**, 643) is still one of the classics on this subject. The most distressing aftermath of intravenous infusions is the frequency with which chills occur. STOKES and BUSMAN (*J. Am. Med. Assn.*, 1920, **74**, 1013) believed that substances in the rubber tubing were responsible for a large number of these. Many other theories have been advanced, but the work of SEIBERT (*Am. J. Physiol.*, 1923, **67**, 90; *Arch. f. exp. Path. u. Pharm.*, 1927, **121**, 247) has been the most promising. This worker had found that certain river bacteria, the split products of which pass over in the distillate, are responsible for most of the chills encountered. RADEMAKER (*Ann. Surg.*, 1930, **92**, 195) has reported a method of distillation of water and preparation of the solutions which has, to a large extent, eliminated the

chills in those institutions which have adopted the method. VINCENT (*J. Pharm. and Exp. Therap.*, 1929, **36**, 107) and HIRSCHFELD, HYMAN and WANGER (*Arch. Int. Med.*, 1931, **47**, 259) have pointed out the dangers of rapidly introducing a large amount of fluid in the blood stream. The latter authors were able to produce chills, a fall in the blood pressure and an increase in the pulse rate by the rapid introduction of saline solutions intravenously. When the same solutions were given slowly no such untoward effects were encountered. These results indicate the advantages of the slow continuous intravenous drip. MATAS (*Ann. Surg.*, 1924, **79**, 643), HENDON (*Med. Arts and Indianapolis Med. J.*, 1931, **34**, 491), AUSTIN and RAVDIN (*Trans. Coll. Phys.*, Philadelphia, 1931, **53**, 10) and HORSLEY (*Arch. Surg.*, 1931, **22**, 86) have written on the advantages of the slow continuous intravenous drip. In each individual patient the clinician must first determine the needs of the patient from the standpoint of total fluid, salt and glucose and then make use of the methods of administration available to accomplish the desired result in the particular patient.

THERAPEUTICS

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Studies on the Treatment of Diabetes by Diathermy of the Pancreas.—It having been shown experimentally that diathermy is capable of increasing the activity of many of the glands of internal secretion, including the pancreas in experimental animals, RAUSCH (*Deutsch. med. Wchnschr.*, 1932, **58**, 1244) applied diathermy as a therapeutic measure in 12 patients with diabetes of varying degrees of severity. In every instance the patient was under adequate control both as to his consumption and his utilization of carbohydrate. The author concludes that in mild cases diathermy has the most favorable results. In such cases its systematic application significantly raises sugar tolerance, even permitting the patient to use greater quantities of carbohydrate than the minimum required so that he may carry on efficiently. The increase in pancreatic activity may even permit the patient to go without the use of insulin. In cases of medium severity the therapeutic value of diathermy is less, for sugar tolerance is only moderately increased, the greatest extent being such as to permit the patient to omit up to about 40 units of insulin. In advanced cases the best that can be hoped for from diathermy is a small reduction in the required dose of insulin. The mechanism by which diathermy produces these effects is believed to be that of increase in insulin production as a result of local improve-

ment of circulation in the pancreas with secondary increase in the activity of the islands of Langerhans. The author obtains the best results when an electrode of 60 sq. cm. of area is applied over the pancreas region combined with one of 100 sq. cm. applied to the abdomen. The intensity of current should be raised to a point of maximal heat tolerance and the duration of treatment should be from ½ to 1 hour, preferably the latter in the majority of cases.

Clinical Comparison of Ergotoxin and Ergotamin.—Notwithstanding the great interest in the chemistry and pharmacology of ergot and its various constituents, there remains considerable uncertainty both as to the clinical action of the alkaloids isolated, as well as to the other constituents present in the crude drug. At the request of the Therapeutic Trials Committee of the Medical Research Council of Great Britain, MOIR (*Brit. Med. J.*, 1932, **1**, 1022) undertook to study the clinical effects of ergotoxin ethanesulphonate and ergotamin tartrate (gynergen). As these alkaloids are not used during partuition, but in puerperium, a bag was introduced into the uterus usually at the 7th day of the puerperium. The bag was connected with tubing to a mercury manometer, and this, in turn, was fitted with a float by means of which variations of intrauterine pressure were recorded on a drum. A different patient was used for each test. Twenty-five cases were given either ergotoxin or ergotamin. The ergotoxin salt was tested in 0.25 mg. intravenous, 0.25, 0.5 and 1 mg. intramuscular and 1, 2 and 2.5 mg. oral doses. The ergotamin salt was administered in 0.25 and 0.5 mg. intravenous, 0.25, 0.5 and 1 mg. intramuscular and in 1.5, 2 and 3 mg. oral doses. Both alkaloids were found to be very active in stimulating uterine contractions. After the intravenous doses 4 to 10 minutes elapsed before the onset of contraction; after intramuscular injection 15 to 45 minutes were required. The effect of the oral doses was erratic. After the larger doses the contraction came at about 1-minute intervals. The duration of the effect was in excess of 3 hours. The effect of the alkaloids on the cardiovascular system was not studied. No serious side effects were observed. Three patients complained of a feeling of depression and weight in the head, and 1 patient of nausea and headache. It is concluded that the optimal dosage of both ergotoxin and ergotamin was 0.5 mg. intramuscularly. Doubling this dosage produced but slight increase in action. The observations presented show that ergotamin and ergotoxin are indistinguishable from each other in their clinical actions.

Comparative Studies on Adrenalin, Sympatol and Ephetonal.—The existing confusion as to the relative actions of these three somewhat similarly acting substances upon the pulse, blood pressure and blood sugar lead E. SCHILLING and GERTA KOPP (*Deutsch. med. Wchnschr.*, 1932, **58**, 1399) to present the results of a series of parallel observations carried out upon patients. The intramuscular injection of adrenalin in doses of 0.7 to 1 mg. regularly produces a marked rise of blood pressure, blood sugar and pulse rate which persists on the average for more than 2 hours. The similar administration of sympatol in doses of 180 to 240 mg., on the other hand, causes only a very mild and brief rise in blood pressure and blood sugar without detectable influence upon

the pulse rate. Doses of from 1 to 2 grams of sympatol administered orally are without demonstrable effect. Ephetonal given in quantities of 100 mg. orally manifests slight adrenalin-like actions on blood pressure, blood sugar and pulse, but the reactions from such doses are weaker than those which follow the intramuscular injection of 1 mg. of adrenalin.

The Experimental Basis for the Treatment of Bronchitis With Ether According to Bier.—The pharmacologist, T. GORDONOFF, (*Deutsch. med. Wchnschr.*, 1932, **58**, 1358) presents the results of his own experiments as well as those of others, in support of the validity of Bier's recommendation of the use of ether in the treatment of bronchitis, particularly the postanesthetic variety. The dose recommended by Bier is 0.5 cc. of ether administered frequently by hypodermic injection. Ether thus employed should be classed as a true expectorant. In the course of its excretion through the lungs it increases respiration, dilates the lung capillaries, produces a slight rise in blood pressure and causes increased blood flow through the lungs. It also increases both the quantity and fluidity of bronchial secretion and apparently in many cases actually enhances the rate at which bronchial secretion is transported out of the lungs by way of the trachea. Combined with the foregoing actions ether exerts an insignificant bactericidal and a more marked bacteriostatic action and probably somewhat facilitates phagocytosis. The author concludes that from an experimental basis ether merits the rank of being peculiarly effective expectorant.

PEDIATRICS

UNDER THE CHARGE OF

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Juvenile Acrodynia: Report of 11 Cases.—CRAWFORD (*Arch. Derm. and Syphilol.*, 1932, **26**, 238) states that infantile or juvenile acrodynia is a striking disease syndrome of the neuromuscular and mucocutaneous systems. It has been recognized in Australia for the past 40 years, but only for the past 15 years in the United States and for the past 12 years in Canada. The first cases in England, where it is often called Swift's disease, were those reported by Doak. In continental Europe it was first reported by Feer of Zürich in 1923, and it is often called Feer's disease. It affects infants and children from 2 months to 2 years of age, and occasionally older children and adults. The ages of the majority of the children affected are between 1 and 2 years. Males and females are affected equally. Although all of the cases of this report were white children, some suspected cases have been seen in negro children. The disease lasts from 6 weeks to 1 year. Relapses after a few weeks or months of recovery are frequent. The mortality rate ranges between 5 and 10 per cent. The prognosis should always be guarded as sudden and unexpected deaths occur. The victims are highly susceptible to

pneumonia, which often terminates fatally. In this series the mortality rate was 36 per cent and was due chiefly to pneumonia. The treatment is difficult as there is no specific remedy and symptomatic treatment is of little avail. Sedative drugs are of no value. Feeding is of the greatest importance, as those receiving regular nourishing food usually do well, while those whose diets are inadequate or who refuse food do poorly. Gavage must be used if necessary. Foods rich in vitamins A and B are indicated, and abundant orange and tomato juice, yeast and cod-liver oil seem to be beneficial. A diet of liver has been advocated on the basis that it contains a definite curative factor. Ultraviolet irradiation is of no value. Cold applications to the skin give the most relief. Calamine lotion made up in camphor water is soothing to the general cutaneous surface. Cold wet dressings of 1 per cent boric acid solution, physiologic salt solution, Ringer's solution or very dilute solutions of aluminum acetate to the extremities and the genitalia are soothing. Daily application of olive oil or ointment of rose water tend to keep the skin soft and to prevent dryness.

The Leukocytic Response to Measles.—BENJAMIN and WARD (*Am. J. Dis. Child.*, 1932, **44**, 921) studied the leukocytic reactions in 46 cases of measles, including observations on 20 cases during the period of incubation. They used the supravital technique and the analysis was based on the use of a table of normal values for each of the white cell elements during the different ages of childhood. During the incubation period the variations in the numbers of leukocytes was relatively slight. On the first day of the prodromal stage the leukocytic picture showed striking alteration, manifested principally by a fall in the number of lymphocytes. At the height of disease all of the cell elements contribute in the production of a leukopenia. Histologic changes observed in the lymph nodes obtained from one of the patients indicated that the development of the lymphopenia in measles was coincident with marked hyperplasia of the lymphoid tissues. The young leukocytes in the glands did not appear in great numbers in the blood stream until the beginning of convalescence. The onset of the prodromal period of measles is peculiar in that there is usually a fever of quite marked degree with little other evidence of illness. At the same time the blood picture undergoes a marked change that is quite out of proportion to the clinically mild appearance of the illness. This is a point very highly suggestive of measles.

Antitoxin Content of the Blood Serum of Children With Negative Reactions to the Schick Test.—MESSELOFF and KARSH (*Am. J. Dis. Child.*, 1932, **44**, 999) titrated the blood of 51 children with negative Schick reactions for the antitoxin content. Forty-eight (94 per cent) had at least $\frac{1}{30}$ unit of antitoxin per cubic centimeter of blood serum. In 1 case this value was between $\frac{1}{50}$ and $\frac{1}{100}$ unit, and in 2 other cases between $\frac{1}{30}$ and $\frac{1}{5}$ unit per cubic centimeter of serum. They did not find any child with a negative reaction to the Schick test with no antitoxin in the blood. In cases reported with negative Schick reactions with little or no antitoxin in the blood, this discrepancy has in all probability resulted from the use of a toxin of questionable potency in making

the test. A standardized, potent toxin is essential for obtaining consistently correct results. In certain individuals a reaction to the Schick test will be positive in from 24 to 48 hours, but will become negative after that time. This type of reaction is found in those having less than the usual $\frac{1}{30}$ unit of antitoxin per cubic centimeter of serum. From the standpoint of immunity against diphtheria such individuals present no great problem, as they possess usually sufficient immunity to protect them against the development of diphtheria. As a rule the Schick test when correctly performed with an efficient material is a practical and reliable indicator of the presence of diphtheria antitoxin in the blood in an amount sufficient to protect the individual against clinical diphtheria.

The Prevention of Rickets.—MITCHELL and COLEY (*J. Am. Med. Assn.*, 1932, **99**, 1768) began their study with a group of 250 babies, but by the time their second birthdays had been reached, the group had been narrowed down to 139 who had continued under observation. Of these, 31 (22.3 per cent) at some time during the study showed clinical evidence of rickets. In a control group the total incidence of rickets in the first 2 years of life was 54.2 per cent. On at least 1 Roentgen examination the condition in 22 (15.9 per cent) was diagnosed as rachitic. The difference between the number of positive findings on clinical and on Roentgen examination compared favorably with the observations as reported by others. Two reasons are given as an explanation of the high incidence in this series as compared with that given by other observers. This first is that these cases were studied over a longer period as compared to a few months in other series. The second is that the second year is considered and as was shown in an earlier report the highest percentage of positive results were seen during the second year. In most other reports the observations were begun and ended prior to the end of the first year. An additional factor is the inclusion of all children who at any time showed clinical or Roentgen evidence of rickets. Either cod-liver oil, in doses of 2 or 3 teaspoonfuls daily, or viosterol, in doses of 8 to 10 drops daily, exerts a definite influence against the development of rickets, and by either treatment severe or even moderately marked rickets may be prevented in babies who live under good conditions of hygiene. In spite of this treatment, 22.3 per cent of patients showed clinically mild rickets. In 51.9 per cent of the cases Roentgen findings were positive. The administration of cod-liver oil as mentioned before protected 82 per cent of the patients, while the dose of viosterol mentioned completely protects only 75 per cent, in spite of the fact that the amount of viosterol has a little more than twice the amount of vitamin D contained in the daily dose of cod-liver oil. The lowest prevalence of rickets, 9.9 per cent, occurred among those given sunbaths in summer and viosterol and cod-liver oil in winter. The ultraviolet irradiation proved a satisfactory substitute for the sunbaths. In the causation of rickets there must be other factors than a deficiency of vitamin D such as a comparative deficiency of vitamin A, a deficiency of minerals in the diet, or perhaps some other as yet unrecognized agent in which the influence of light plays as important a part as it does in the activation of ergosterol.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF
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Lymphogranulomatosis Inguinale, or Durand-Nicolas-Favre Disease.—An increasing amount of attention has been focused on this so-called fourth venereal disease in the past few years, and ZAKON (*Arch. Dermat. and Syph.*, 1932, **26**, 238) gives an excellent review of its literature, outlines the clinical features and reports 3 additional cases. Lymphogranulomatosis inguinale is a subacute indolent inguinal adenitis of venereal origin which begins as a solitary nodular, papular or herpetiform lesion on the surface of the prepuce or in the coronary sulcus. An intraurethral erosion may initiate the process. The initial lesion is characterized by its small size, nonpainful character and its evanescence, and is followed within an average period of from 2 to 3 weeks by a progressive inguinal adenitis and mild constitutional symptoms. The glands become more and more adherent to the skin, which breaks down to produce sinuses exuding primarily a small amount of sticky pus which becomes more abundant as secondary infection occurs. The etiologic factor is undetermined. A specific diagnostic test for lymphogranulomatosis inguinale was introduced by Frei in 1925. The antigen is prepared from pus obtained by puncture of the buboes. The material is diluted 5 to 10 times with physiologic salt solution, heated at 60° C. for 2 hours on 1 day and for 1 hour the next day, and subjected to the usual tests for sterility. One-tenth cubic centimeter of this antigen is injected intracutaneously, a positive test consisting of a reddish, infiltrated papule which appears within 48 hours. A positive reaction may be delayed for 8 or 10 weeks after the onset of the affection but can be obtained months or even years after the appearance of the adenitis.

Erythema Nodosum.—An organism of the genus Corynebacterium has been cultivated from the subcutaneous tissue in each of 3 cases of erythema nodosum by MOON and STAUSS (*Arch. Dermat. and Syph.*, 1932, **26**, 78). In a case of unusual severity the organism was also cultivated from the blood stream. In 13 of 14 inoculated animals lesions were produced that had the histologic appearance of erythema nodosum, and the same organism was recovered in cultures from these lesions. The authors believe that the organism found in the reported cases is identical with that described by Rosenow and suggest that it be designated Corynebacterium cutis-nodosæ.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Histogenesis of Papillary Ovarian Cysts.—The exact origin of papillary cysts of the ovary has never been definitely determined, although many theories have been advanced. This subject has been investigated histologically at The Mayo Clinic by McCarty (*Surg., Gynec. and Obst.*, 1932, **54**, 188), who found small, cortical, epithelial structures of a cystic nature in 100 per cent of the grossly normal ovaries which were removed with papillary ovarian cysts of the opposite side, whereas in the normal control group the structures were found in only 64 per cent of the cases. These structures are of germinal epithelial origin. The superficial papillomata were found about twice as frequently in grossly normal ovaries which had been removed with intracystic papillary ovarian cysts of the opposite ovary, as in the ovaries from normal controls. From the microscopic appearance it would seem that these structures are closely related to the papillary ovarian cysts. In this series of cases very little evidence was obtained to indicate that the Graafian follicles or the rete of the ovary are frequent sources of origin of the papillary ovarian cyst. Therefore, he believes that it may be stated: (1) That most papillary ovarian cysts probably develop from the small germinal epithelial cystic structures found in the cortex of the normal ovary, and (2) that the grossly normal ovary which is found in association with an intracystic papillary ovarian cyst of the opposite ovary is a potential danger and should always be removed, age permitting. This study reinforces from the laboratory what most operating gynecologists have believed for many years, namely, that in the presence of a papillary cyst of one ovary, it is usually good judgment to remove both ovaries in order to forestall the probable future trouble in the remaining ovary even though apparently healthy at the time.

Postmenopausal Bleeding.—Vaginal bleeding occurring after the menopause should never be disregarded by either the patient or the attending physician until the etiologic factor has been determined. While in the majority of cases the bleeding is caused by some type of carcinoma it is not always due to this cause. In a survey of 98 cases of bleeding of this type which was made by Kanter and Klawans (*Am. J. Obst. and Gynec.*, 1932, **24**, 192), the cause was found to be, in order of frequency, carcinoma (67 cases), cervical polyps (8 cases), fibromyomas (7 cases), uterine prolapse (5 cases), senile vaginitis (3 cases), cervical erosion (3 cases), urethral caruncle (2 cases), uterine

fibrosis (2 cases), and nonspecific ulcer of the vagina (1 case). Of the 67 carcinomas in the series, 51 were cervical, 11 were fundal, 2 were on the vulva, 1 was in the vagina and 2 were ovarian. In the series therefore, 68.4 per cent of the cases were of a malignant nature and 31.6 per cent were benign, so that the axiom "all cases of postmenopausal bleeding should be considered as malignant until proved otherwise" is very significant. They emphasize that once the menopause has been definitely established (no menses for a period of from 6 months to a year) all bleeding from the genitals should be considered as abnormal since there is no apparent relationship between the type or amount of bleeding and the seriousness of the existing condition. From their survey they also feel that parity, length of time in the menopause and the duration of active menstrual life are of no particular value as diagnostic aids.

Myoma Operations During Pregnancy.—This subject which is one of frequent discussion has been summarized by MAYER (*Zentralbl. f. Gyn.*, 1932, **56**, 1922) of Tübingen by stating that there are three ways of handling this complication: (1) By extreme conservatism, with consideration only for the life of the fetus; (2) consideration only of the patient and having little regard for the continuation of the pregnancy, and (3) taking into consideration the interest of both mother and child as described below. As long as the myoma and the pregnancy give no great amount of trouble, they should be left alone. However, if the tumor gives much pain, so that if pregnancy were not present operation would be indicated, the existence of an associated pregnancy is not an absolute contraindication against operation. If operation be undertaken it should not consist of hysterectomy but rather myomectomy with preservation of the pregnancy. Only rarely does the patient abort after myomectomy but, even if this should occur, at least the uterus is preserved for future pregnancy.

Effect of Knee-chest Position.—In order to determine whether the knee-chest position during the postpartum period accomplishes all that has been claimed for it, SCHAUFFLER (*J. Am. Med. Assn.*, 1932, **99**, 726) has made some controlled observations which tend to contradict generally accepted opinions. Following delivery the uterus is normally in a position approximating first-degree retroversion. Theoretically, this tendency is increased through the dorsal posture of the patient in bed, which is more or less routine. The natural tendency of the heavy corpus to drop back against the sacral promontory is thus accentuated. One would naturally suppose that a ventral posture favoring a dropping forward of the heavy corpus would aid the natural forces, but unfortunately the observations in this study constitute a definite and surprising contradiction to this belief. This series of 169 patients were nearly all vigorous young women (about 90 per cent primiparous) and presented a group practically free from complicating factors such as retroversion from previous pregnancy, prolapse and the like. Alternate patients were put on a special regimen consisting of the ventral posture in bed, and the knee-chest position beginning on the 8th day postpartum and increasing to 20 minutes twice a day. On the 18th day they were

started on the camel walk, and instructed to rest as nearly as possible entirely on the abdomen while in the prone position. The other half of the group were given no exercises whatever. The incidence of retroversion following the knee-chest position was 47.2 per cent as opposed to 34.5 per cent for the group which did not assume this position. It may be unfair to conclude that the use of the knee-chest position actually increases the incidence of postpartum retroversion, but Schauffler believes that the confidence that has always been placed in it as a therapeutic measure is no longer justified.

OPHTHALMOLOGY

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Classification of the Optic Atrophies.—PATON (*Proc. Roy. Soc. Med.*, 1930, **24**, 25) thinks that atrophies of the optic nerve should be classified into those of localized origin, those of diffuse or indeterminate origin and those of unknown origin. The atrophies of localized origin may be retinal, papillary or retrobulbar. The retrobulbar atrophies may be intraorbital, foraminal or intracranial. In the group of retinal atrophies belong retinitis pigmentosa, amaurotic family idiocy, cerebromacular degeneration, macular without cerebral degeneration and the atrophies secondary to retinal and choroidoretinal inflammations and vascular degenerations. The essential cause of the atrophy of the nerve in these cases is the degeneration of the ganglion cells of the retina. Certain of the toxic amblyopias may belong to this group. To the group of papillary atrophies belong glaucoma, cavernous degeneration in high myopia, atrophy secondary to papillitis and papilledema and traumatic avulsion of the optic nerve. As a result of long-standing edema of the disk, the nerve fibers swell, undergo fatty degeneration and are replaced by neuroglial proliferation which in its contraction squeezes out the remaining intact nerve fibers. Added to this is the obliteration of the smaller vessel channels by endothelial proliferation. An atrophy of the intraorbital retrobulbar type is the result of an inflammation affecting the parenchyma of the nerve directly or extending inward from the meninges. The commonest cause of parenchymatous inflammation is disseminated sclerosis, but postinfluenzal, syphilitic, postherpetic and other types of myelitis can occur. The interstitial or meningitic type of atrophy may result from septic, tuberculous or syphilitic meningitis, or from orbital inflammations secondary to sinus infections or dental abscesses. Intraneural or extraneural tumors in the orbit can also cause retrobulbar atrophy. The foraminal type

of retrobulbar atrophy is most commonly seen in head injuries, the trauma not necessarily involving the foramen directly in a fracture but resulting in nerve tears and hemorrhages into the nerve sheaths. It occurs also in Paget's disease, in leontiasis ossea and in osteitis deformans. The field changes in these cases are very irregular, peripheral contractions, ring scotomata and paracentral scotomata. Sclerotic changes in the ophthalmic artery as it passes through the foramen may cause a similar type of atrophy. The intracranial type of retrobulbar atrophy is most often due to tumors in the pituitary or suprapituitary regions, on the base of the frontal lobe, or at the anterior end of the temporosphenoidal lobe. Disseminated sclerosis and meningitis also may cause this type of atrophy, as well as basal aneurysms, and sclerotic changes in the internal carotid. The site of the primary affection of the optic nerve is not definitely known in the atrophies due to general toxins such as tobacco, methyl alcohol, carbon bisulphid, diabetes and the anemias. It may be in the ganglion cells of the retina or in the nerve fibers behind the globe. Quinin and aspidium filixmas produce retinal arterial spasm and secondary retinal atrophy. Arsenic apparently affects the nerve fibers directly. Lead acts on the nerve fibers directly or indirectly through arterial degenerations. Among the atrophies of unknown origin must be placed Leber's familial atrophy and the atrophies associated with degenerations of the central nervous system, such as Friedreich's disease, peroneal atrophy and hereditary cerebellar atrophy. Tabetic atrophy is partly interstitial and partly parenchymatous in type. Either element may predominate in a given case, with corresponding differences in the course of the atrophy. Thus the onset may be gradual with segmental losses in the peripheral fields, but with fair preservation of central visual acuity over a long period; or rather rapid loss of central visual acuity and of color fields may occur while the peripheral fields for white are well preserved. The atrophic process commences, as a general rule, in the proximal and not in the distal or peripheral portion of the optic nerve.

Pathogenesis of Retinitis Pigmentosa.—For the study of pigmentary degeneration of the retina in its relationship to the local pathogenesis of retinitis pigmentosa, FRIEDENWALD and CHAN (*Arch. Ophth.*, 1932, **8**, 173) injected suspensions of washed melanin granules obtained from the retinal pigment epithelium of cows' and pigs' eyes into the vitreous of albino rabbits. Clinically, after several weeks, some of the pigment was seen to have entered the retina, at first in the periphery, and later near the optic disk where it usually arranged itself around the blood-vessels as in retinitis pigmentosa. Histologically, in eyes enucleated 4 to 6 months after the injection monocytic phagocytes containing pigment were found in the vitreous and on the surface of and in the retina. Müller's cells and fibers were also found to be packed with pigment. In eyes enucleated at longer periods after injection Müller's fibers were found to be markedly proliferated and the retinal tissues were found to be markedly disorganized in the regions where the phagocytosis of pigment was most active. The damage was greatest in the ganglion cells, and next in the neuroepithelium. In regions in which pigment was present in the retina but had not been phagocytosed the retinal

cells were not damaged. It seemed, therefore, that the destruction of the retinal cells was due to the passage of active phagocytes through the retina for the removal of the pigment granules. It seems probable that in retinitis pigmentosa there is a continuous discharge of pigment into the retina and that the resultant phagocytic invasion of the retina produces the destruction of the retinal elements, the overgrowth of Müller's fibers, and the secondary atrophy of the optic nerves. Whether the primary lesion lies in the pigment epithelium itself or in the neuro-epithelium is still a matter of conjecture.

RADIOLOGY

UNDER THE CHARGE OF
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Encephalography in Children.—ELEY and VOGT (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 686) regard encephalography as a valuable diagnostic procedure in the study of fixed lesions of the brain in children. Its principal contraindication is increased intracranial pressure as evidenced by papilledema, etc. Although the encephalogram gives a definite impression of the gross pathologic condition, it will not determine the cause of the pathologic changes. Trauma, hemorrhage, developmental defects and infections all produce pathologic changes which ultimately are similar in the encephalogram. Little is known concerning the size of the subarachnoid space in normal infants and children, and though certain normal standards are accepted, there are frequent occasions when the maskings are equivocal. The authors believe that probably one of the most important uses of encephalography will be its employment in the selection of cases of epilepsy suitable for treatment.

The Roentgen Findings in Chronic Progressive Bulbar Palsy.—The earliest symptom of bulbar palsy is difficulty in swallowing and this is likely to bring the patient to the roentgenologist. CHRISTIE (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 717) has recently observed an instance in a man, aged 27 years, who for 2 years had had difficulty in swallowing. It was possible with complete extension of the head to swallow small quantities of water, but large quantities could not pass and produced choking. The Roentgen examination showed a delay in swallowing taking place entirely in the pharynx. Fluid was almost immediately regurgitated and some of it entered the larynx causing the patient to cough. Only a very small amount passed into the esophagus. There was no evidence of a foreign body or of any lesion reducing the lumen of the pharynx or esophagus, and the lungs, pleura

and mediastinum were negative. On neurologic examination a diagnosis of bulbar palsy was made. Among early symptoms which may be suggestive to the roentgenologist are slight blurring of speech, inability to pucker the lips and a nasal voice.

Agranulocytic Angina.—Agranulocytosis, a term used to designate a condition in which the granular elements of the blood are lacking, was first described by Schultz, in 1922. This blood dyscrasia is usually an accompaniment of severe throat lesions, and Friedemann suggested the designation of angina agranulocytica. The disease occurs chiefly in middle-aged women, and prior to the employment of Roentgen therapy the mortality was as high as 91 per cent. By irradiation in small doses in conjunction with blood transfusion and other measures the mortality has been lowered. WATERS and FIROR (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 740) treated 5 cases with small doses directed to the marrow of the long bones. Three patients recovered, and this experience together with the results of animal experimentation conducted by the authors seems to warrant further employment of the method.

A Roentgenographic Study of Glass and Its Visibility as a Foreign Body.—LEWIS (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 853) has investigated the very practical question of whether glass particles embedded in the body can be revealed with Roentgen rays. Grouped according to their permeability by the rays, glass is of two classes: (1) ordinary and (2) lead and barium glass. Lead and barium glass are used occasionally for lenses, crystal table ware, art ware, tubing, thermometers and electric light bulbs. A particle of lead or barium glass, even smaller than 2 mm. in diameter, lodged anywhere in the soft tissues of the body, might be expected to be shown by thorough roentgenographic study. Most of the glass which might be encountered as a foreign body, such as window glass, automobile glass, fragments of bottles or clinical thermometers, etc., belongs in the ordinary group. Nevertheless a particle of ordinary glass might be expected to be shown clearly in the soft tissues of the upper extremity or leg, and under favorable conditions in the thigh, abdomen or pelvis.

The Roentgen Signs of Tuberculosis of the Vertebral Body.—One hundred cases of tuberculosis of the spine were studied by DAUB and BADGLEY (*Am. J. Roent. and Rad. Therap.*, 1932, **27**, 827). The average age of the patients was 29 years and the average duration of symptoms at the time of examination was 6½ years. Roentgenologically the following types are to be distinguished: (1) Central, (2) intervertebral articular and (3) anterior. The central type is more common in the dorsal area, and the intervertebral in the lumbar segment. The central variety causes collapse of the vertebral body in a high percentage of cases, while the body is preserved until late in the disease in the intervertebral type. Narrowing of the disk is the earliest and most constant sign in tuberculosis of the spine. Abscess is the most common complication and was found in 84 per cent of this series. Skipped infection, or 2 foci of infection with normal vertebræ between, was found in 10 per cent of the cases. Concomitant tuberculosis in other parts of the body was present in 53 instances; pulmonary lesions were most common and occurred in 24 cases.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF
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Psychological Factors in the Prevention and Treatment of Alcohol and Drug Addiction.—REES (*Lancet*, 1932, **2**, 929) states that alcoholism and drug addiction are in almost every case the symptoms of a psychologic maladjustment; a relief from a sense of oppression at having to stand up to the circumstances of life. This habit is usually developed from the spoiled and indulged child who meets difficulty when he comes into the world as an adult, those with an inferiority complex resulting from a previous sense of superiority, the self-conscious, who can by it gain courage, forgetfulness, and put themselves more in tune with life. The aim of the treatment should be the discovery of the cause of the maladjustment so that the patient can be gotten to see and realize his own problem. Methods of psychotherapeutic approach are persuasion, suggestion and mental analysis, necessitating a doctor with a great deal of insight and a great interest in the personality of his patient. Increased knowledge on the part of the doctors as to the ways in which neurotic tendencies arise in the individual will help in the future in producing a better-balanced and adjusted race, not requiring the wrong use of drugs. Much is being done by emphasizing the advantages of right living and thinking, and by inculcating the courage and the spirit of adventure, which is better than emphasizing warnings and prohibitions. Parental education is being undertaken which means wiser and more understanding treatment of the child in the early years.

Suicide: Social, Forensic and Psychological Aspects.—MAJOR C. R. BELL (*Milit. Surg.*, 1932, **71**, 399). *Sociologic aspects:* SIR HUBERT BOND reports no history of suicide before the 18th century, omitting Biblical, classical and medieval references. The average number of successful suicides in England and Wales each year is about 5000; of these only about 50 occur in the certified insane. There is an increase in the number of attempted suicides reported, which is short of the real total. During the census years, 1901, 1911, 1921, the suicide rate per 10,000 population was 1 for both sexes and for 1929, 1.3 for both sexes. Sir Hubert gives proportions of suicides as to sex and the means of suicide as to sex. Women have a higher percentage with jumping from high places, drowning, poisoning; men, use of cutting or piercing instruments, hanging or strangulation, crushing and use of firearms. Since 1921 an increase in the use of coal gas by inhalation has occurred, due largely to the nature of its action and its ready availability. *The forensic aspect:* W. N. EAST asserts that suicide

connotes to the legalist a crime and to the physician a state of emotional disorder. It was originally an ecclesiastical offense. The ancient custom was to bury a suicide at a crossroads with a stake driven through his body, and in the early 13th century a person who committed suicide in order to avoid conviction for a crime forfeited his lands. Suicide in English law is a felony—self-murder, and the recovered offender may be committed for trial and punished by imprisonment with hard labor. An analysis of 1000 consecutive cases of attempted suicide showed only about one-fifth were certifiable insane, but many suffered from temporary mental disorder. These are detained indefinitely for observation and treatment. *Psychologic aspect:* H. CRICHTON-MILLER believes that the majority of suicides are not acts of the insane, but man's retreat from life and reality. Underlying motives are: (1) Physical pain, or anticipated pain or insanity, and frustration of instinctive demands, especially of the sex instinct. (2) Social sufferings and fears —the bankrupts, those out of employment, or facing exposure of misdeeds, remorse for wrongs committed, illegitimate pregnancy, those with an "inherited tendency" for suicide. (3) Doubts and fears of the hereafter. In some social systems self-destruction under certain circumstances is regarded as a virtuous act. Other cases are self-punishment, the supreme sacrifice for some redemptive purpose, melancholics and cyclathymics. The majority of people committing suicide are not the insane but the "borderline insane," the "deviate" and the "psychopathic."

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Stem Cell of the Monocyte.—RINEHART (*Arch. Path.*, 1932, **6**, 889) made use of a previously described (*Anat. Rec.*, 1932, **52**, 151) method of silver impregnation of blood films in attempting to trace the nuclear development of the monocyte from its parent cell. Studies reported were carried on with blood obtained from a human case of monocytic leukemia, studied during a period of 18 days, from hospital admission until death. Mature monocytes ranged from 72 to 96 per cent, young monocytes from 2 to 20 per cent, and monoblasts from 1 to 5 per cent; the total white count running between 34,000 and 150,000. A small number of cells were observed, corresponding in nuclear architecture to the hemohistioblast of Ferrata. Many, with nuclear structure intermediate in form between the hemohistioblast and monocyte were noted. In a single blood film, cells representing all gradations in the transformation from hemohistioblast to mature monocyte were

present. The results are in accord with those of Ferrata and coworkers, and further, favor the view held by Cunningham, Sabin and Doan, "that the precursor of the monocyte is an undifferentiated mesenchymal cell."

Experimental Production of Sidero-fibrotic Lesions in the Spleen.—FASIANI and OSELLADORE (*Virch. Arch. f. path. Anat.*, 1932, **284**, 474) report an experimental study of that peculiar lesion of the human spleen which has been variously referred to as mycosis, calcium-iron incrustation, siderofibrosis, and Gandy's or Gandy-gamma nodules. To the naked eye the lesions appear as tobacco-colored cicatricial flecks on the cut surface of the spleen, usually with a depressed puckering of the overlying capsule. Microscopically the lesion is seen to be within a trabeculum in close relationship to the larger bloodvessels and is characterized by a tangled fibrous core with a hemorrhagic zone around the periphery. The central part contains (1) peculiar fibrillar or rodlike structures, not infrequently segmented like mycelia; some of these are deeply basophilic, others remain pale; (2) tiny basophilic spherules, somewhat like spore forms of a yeast organism, sometimes concentrically laminated; (3) occasional foreign-body giant cells. In the rodlike formations and spherules, iron and calcium in varying proportions are demonstrable by special stains. These structures, because of their resemblance to fungoid organisms were thought by some authors to represent a parasitic cause of the lesion but the authors of this article regard the parasitic theory as disproven. They succeeded in reproducing the lesion in dogs by first producing congestion through partial ligation of the splenic vessels, and then traumatizing certain areas of the spleen with electrocautery or injections of calcium chlorid. It was noteworthy that while the experiment succeeded with dogs, rabbits and cats gave negative results though treated in exactly the same manner. The authors regard the lesion as one which results from circumscribed degenerative or necrotic foci occurring in a spleen through which the blood flow is impeded. They look upon the mycelia-like forms and the round bodies as inert products of degeneration formed of tissue remnants. Now that a means has been devised of producing the lesion experimentally the way is opened for investigation of the causation of the lesion in the human spleen.

Marrow Hyperplasia and Hemoglobin Reserve in Experimental Anemia Due to Bleeding.—OEHLBECK, ROBSCHEIT-ROBBINS and WHIPPLE (*J. Exp. Med.*, 1932, **56**, 425) detail the results obtained and conclusions drawn from observations conducted upon 18 dogs whose blood hemoglobin level was kept at 40 to 50 per cent by repeated bloodletting (instead of the normal 140 to 150 per cent) for varying periods: from 1 year and 4 months to 7 years and 4 months. As the dogs died, of anesthesia, natural causes, or accident, they were autopsied, and all vertebræ, ribs and long bones split and examined. In but 2 was there evidence of marrow exhaustion. Many showed red marrow spread, but strangely there was no relation between the amount of hemoglobin produced in life and the degree of marrow spread encountered post-

mortem. Changes in other organs included those of senility for the most part. The splenic pulp showed erythrogenesis, but to a small degree. There was no evidence of marrow metaplasia in the livers. In dogs possessing a theoretical hemoglobin reserve, its existence in the form of red cells in the marrow was not evident. Three of the dogs, that had been splenectomized, presented no change in morphologic manifestations or course of the anemia. It was notable that all of the dogs remained in remarkable health despite the prolonged, oft-repeated loss of blood.

The Etiology of Colds.—The common cold has long been recognized as not only the cause of great discomfort and loss of time but as the preliminary stage of many of the more serious diseases of the respiratory tract. It has been found extremely difficult to arrive at any logical conception applicable to even the majority of cases as to the etiologic agent or agents which might be held responsible for the variety of manifestations. WALKER (*Ann. Int. Med.*, 1932, **5**, 1526) has shown that the reported experiments relating to the hypothesis that colds are due to a filtrable virus are inadequate to support the hypothesis, and because of the numerous disturbing factors, each difficult to control, he doubts whether the hypothesis can be submitted to proper experimental test. He further brings evidence to support the view that bacteria are the extrinsic factors in the etiology suggesting that the reaction may be very similar to that in hay fever but in addition the etiologic agents possess the power of multiplication and of tissue invasion—merely the late appearance of an organism in cultures being insufficient to displace it from the position of primary etiology. HILDING (*Ann. Int. Med.*, 1932, **6**, 227) has studied the problem from the physiologic aspect and described four defenses of the upper respiratory tract: ciliary action, exchange of mucin, regeneration and adaptability. The epithelium he showed to be dynamic and intensely active, the cilia moving tremendous loads of mucin and foreign material, the layer of mucin—resembling another lining membrane—is frequently changed being moved rapidly over the ciliated areas and more slowly under traction in the non-ciliated regions. Bacteria are removed rapidly in the deeper parts of the nose and this may explain, he believed, the fact of cultures from these parts being so often sterile, the regions where they do lodge in large numbers however, drain very largely through the meatuses, where cultures are not usually taken. He found that the mucosa, when an irritant attacks from the surface, readily sloughs its injured cells before they are dead and replaces them rapidly by prolific regeneration, which he considered as part of the physiologic process. Further, his experiments indicated that the epithelium can radically and rapidly alter its form according to demands made upon it and that the different types of epithelium are merely various forms of the same general respiratory epithelium. It seems obvious to the Reviewer from the above studies, and the experience of clinicians and laboratory workers, that the search for a specific agent of widespread applicability as the fundamental etiologic cause of colds is extremely complicated and it is not easy to even formulate the necessary qualities of such an agent, if such there be.

HYGIENE AND PUBLIC HEALTH

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Purification of the Virus of Vaccinia.—BEHRENS and MORGAN (*J. Infect. Dis.*, 1932, **50**, 277) found that much more acid had to be added to the dermovirus emulsion than to the neurovirus emulsion used in their experiments, in order to coagulate the cellular and scab material, and this probably affected the virus. Less virus would, however, theoretically, be freed in the case of the dermovirus emulsion, because the isoelectric points of the two components are closer together. The isoelectric method of purification is satisfactory for the neurovirus emulsion, but not for the dermovirus. It does, however, serve the purpose of confirming the assumption that the virus obeys colloidal chemical laws. Both the isoelectric and the aluminum gel methods, which were developed by the authors for the purification of the virus of vaccinia, are satisfactory for neurovirus emulsions.

Prevalence of Venereal Disease in New Orleans, La.—CLARK and USILTON (*Pub. Health Rep.*, 1932, **47**, 1187) report that venereal disease prevalence surveys have been made in a number of American cities. The figures run as high as 20 per thousand population for Memphis, Tenn., to as low as 6.8 for New Orleans. The following is the summary of the data on New Orleans: In New Orleans a 1-day census showed that 32 per cent of the physicians had one or more cases of venereal disease under treatment. There was practically an even distribution of cases reported in private practice and in public clinics or other institutions. There were reported 4820 cases of syphilis and gonorrhea under treatment as of the survey date, February 2, 1931, of which 2676 were syphilis and 2144 gonorrhea. The rate was nearly twice as high among the colored population as among the white. The gonorrhea rate for colored females was found to be extremely low. The investigators have no reason to offer for this finding. There are 90 per cent of the private practice cases in the hands of 15 per cent of the physicians. It is thought, perhaps, that the adequate public clinic facilities for treatment of syphilis and gonorrhea are responsible for the fact that there is so much specialization in these diseases among the private practitioners. Although the concentration of these cases in the care of a few physicians greatly assists in the dissemination of the treatment data on venereal diseases, it is felt that here as in other communities many, if not most, of the early infections are seen first by the family physician, and he should be trained in the early recognition, if not specially in the treat-

ment, of these diseases. The ratio of incidence to prevalence of syphilis is nearly twice as high for the males as for the females, whereas for gonorrhea it is quite similar for the two sexes.

New Orleans was found to have a lower venereal disease prevalence rate than any of the other 10 large cities in which a survey was conducted. However, in conjunction with the prevalence survey in New Orleans a study of the amount of treatment given by unauthorized medical sources was found to be very high. It also was found that at least one-half of the whites and 80 per cent of the colored attempted either self-treatment or were treated over the drug store counter before applying to a clinic for treatment. For these reasons there is a question as to whether the apparently low prevalence rate in New Orleans is due entirely to the effectiveness of the control methods and the excellent free public clinic facilities or to other reasons. The authors do feel, however, that very complete returns were made from those coöperating in the study.

Diphtheria Antibodies Transmitted to the Offspring of Immune Guinea Pigs.—RICHARDSON (*J. Immunol.*, 1932, **22**, 351) made measurements of the diphtheria antibodies, antibacterial and antitoxic, in the sera of the offspring of guinea pigs previously immunized with diphtheria filtrate. The data showed that diphtheria antibodies of the antibacterial sort as well as antitoxin are placentally transmitted. The proportion of $\frac{\text{antitoxin antibodies}}{\text{nonantitoxin antibodies}}$ found in the sera of the offspring shortly after birth was comparable to that in the sera of their respective mothers. The sera of a number of families were studied over periods of 60 or more days following the births; the data of these tests showed that the amount of antibodies originally transferred by the mother is the important factor in determining the duration of the passive immunity of the offspring.

An Epidemic of Croupous Pneumonia Caused by Pneumococcus Type I.—STROM (*J. Infect. Dis.*, 1932, **50**, 430) describes an epidemic of lobar croupous pneumonia in an orphanage caused by pneumococcus Type I. Pneumococcus Type I was found in the sputums and in cultures from the nose and throats of the patients during illness and up to 73 days after the crisis. In one case, it was found in a culture from the nose and throat 4 days before the onset of the disease. Of the contacts 33.3 per cent were found to be carriers during the height of the epidemic, and 16.9 per cent, 2½ months later. The strains from the patients were more virulent in mice than those from the carriers. The disease was more prevalent among the older boys than among the younger ones, presumably because the former represented a more rural population than the latter.

Food Poisoning Due to Toxic Substances Formed by Strains of the Cloacæ-Aërogenes Group.—GILBERT, COLEMAN and LAVIANO (*Am. J. Pub. Health*, 1932, **22**, 721) report an outbreak of at least 125 cases of food poisoning extending over 2 successive days in October, 1930. The epidemiologic findings indicated that creampuffs and chocolate eclairs

manufactured by a wholesale bakery had been eaten by all those who became ill. Symptoms, including prolonged vomiting, profuse diarrhea and cramps, but without rise of temperature, developed within 2 or 3 hours after ingestion of the food and generally subsided in from 4 to 10 hours. Cases occurring on the second day were more severe than those of the first day. A strain of bacilli belonging to the cloacæ-aërogenes group was isolated from samples of the pastry filling as well as from fecal specimens from 5 patients. Filtrates of a medium containing ingredients corresponding to those in the cream filling, in which this organism had been grown for 48 hours, were toxic for rabbits and chickens. The toxic substance from these cultures did not seem to be appreciably altered by heating to the boiling point. Staphylococci and other bacteria isolated were studied similarly, but none of the organisms tested showed evidence of toxicity. The presence of poisonous chemicals could not be demonstrated. Examination of the bakery indicated that the food was prepared under cleanly conditions but that the cream filling was left standing at room temperature for several hours before the shells were filled. After being kept in a refrigerator overnight the pastries were distributed over a considerable territory the following day by automobile truck without refrigerating equipment. Thus an opportunity was afforded for bacteria which might have been present to develop and for toxic substances to be produced by them.

Effect of Lead Arsenate Spray on the Composition and Vitamin Content of Oranges.—Nelson and Mottern (*Am. J. Pub. Health.*, 1932, **22**, 587) present data to show that oranges produced by trees sprayed with lead arsenate differ in chemical composition from normal oranges. The most pronounced difference is a reduction in acidity of the juice; there is also a decrease in sucrose with a corresponding increase in invert sugar. The arsenic content of the edible portion of the orange was not changed by spraying the tree with heavy doses of lead arsenate. The authors conclude from the experiments that have been completed that the vitamin C content of heavily sprayed oranges is decreased fully one-third and it may be only one-half of that of unsprayed fruit.

Tularemia: Occurrence in the Sage Hen.—Parker, Philip and Davis (*U. S. Pub. Health Rep.*, 1932, **47**, 479) report on tularemia of birds, not only on account of the interest from the point of view of a new natural host of tularemia infection but also because there is a possibility of human infection from birds. Four cases are mentioned in which the infection seems to have been traceable to game birds. The data also indicate that a bird tick is concerned in the maintenance and transfer of tularemia among lower animals.

The Races of A. Maculipennis.—Hackett, Martini and Missiroli (*Am. J. Hyg.*, 1932, **16**, 137) state that explanation of "anophelism without malaria" and of the fact that, in Europe, malaria incidence does not seem to be in satisfactory correlation with the density of A. maculipennis has been sought in the existence of races of maculipennis with different bionomic characteristics and different potentialities of malaria transmission. Races have been distinguished in France and

in Holland on the basis of average measurements of some structural character, but such a statistical method is not serviceable in identifying individual specimens, or in determining the racial composition of a given maculipennis population. Only pure strains can profitably be compared in this way, and the method gives us no criteria for recognizing a pure strain. On the other hand, by study of the egg markings and structural peculiarities, Falleroni discovered a fundamental division of maculipennis species into two races, and our observations in many areas of Germany and Italy have confirmed and extended this conception. One race (A. maculipennis labranchiæ Falleroni) lays a uniformly dappled egg with relatively small floats posteriorly placed. The egg occurs as a light-gray type in Italy (but never in pure culture) and as a dark-gray type in North Germany, where this race is the only one present in certain areas. The race has been found almost exclusively in low-lying brackish marshes near the sea, or in inland areas where the water has a relatively high salinity. It also occurs in all areas so far studied where malaria is actually or potentially present, and it appears to be relatively more prevalent in dwellings than the other race. It does not go into complete hibernation, but is relatively active in houses and stables throughout the winter even in Northern Europe. In this respect and in others it seems to be the same as A. maculipennis atroparvus v. Thiel. It has definite affinities with A. elutus. The second race (A. maculipennis messeæ Falleroni) lays an egg irregularly pigmented in bars and angular patches but including always two heavy transverse bands just distal to the ends of the float structures, which latter are relatively large and long. This race occurs in inland fresh waters in Italy and Germany, in the proportion of 95 per cent of the entire local maculipennis population, and each variation except pure black has been found in pure strains in several regions. It predominates in nonmalarious areas, frequents stables more than dwellings, and goes into complete hibernation in winter. Structural differences between the eggs, larvæ, and male hypopygia of the two races have been described. The use of the egg as a differentiating character should make it possible to classify maculipennis populations and to determine the bionomics of each race and its relation to the transmission of malaria.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 19, 1932

Surface Properties of Intestinal Bacteria Before and After Serum Sensitization.—ELEANORE W. JOFFE, CHARLES H. HITCHCOCK, and STUART MUDD (Department of Bacteriology, School of Medicine, University of Pennsylvania). Data concerning the surface properties of certain strains of intestinal bacteria are presented. A nonflagellate

typhoid strain, 0901, a Flexner dysentery strain, and a strain of Bacterium enteritidis have been studied in their smooth and rough variants. The enteritidis bacilli were grown on phenol agar to suppress the flagella. The smooth variants carry surface electric charges so low as to be scarcely measurable, but form even suspensions, insensitive to precipitation by salt. The rough variants grow as a sediment and their suspensions are electrolyte-sensitive, but, paradoxically, they have high surface charges.

Sensitization of these intestinal bacteria with specific immune sera gives them cataphoretic properties presumably approaching those of the antibody protein. Sensitization with rabbit antisera has given the maximally sensitized bacteria isoelectric points between pH 4.8 and 5.2; with horse antisera the isoelectric points have been between pH 4.4 and 4.8. These isoelectric points are well on the acid side of those of normal serum globulins. These results suggest that the antibody globulins against bacteria of this group may be more acid than normal globulins rather than more alkaline like those previously described, such as the antipneumococcus globulin.

Application of Volumetric Methods to the Study of Nonaqueous Cystine Solutions.—T. F. LAVINE and G. TOENNIES (Lankenau Research Institute, Philadelphia). A nonaqueous titration method using sodium methylate as the base, thymol blue as the indicator and chloroform as a diluent was applied to a study of cystin perchlorate solutions in acetonitril. On neutralization by sodium methylate, perchloric acid and cystin perchlorate were indicated by a color change from red to yellow, while acetic acid, ammonium ion, hydrocyanic acid and cystin were denoted by a color change from yellow to blue. Acetic anhydrid in chloroform is also quantitatively neutralized by sodium methylate, mol for mol, the color change of thymol blue being from yellow to blue. The sodium perchlorate formed in the neutralization of perchloric acid was found to affect the first end point leading to low results when the concentration was greater than 0.02 normal.

It was found by titration that acetic anhydrid removes all of the water from a tenth normal cystin perchlorate solution in acetonitril made by the use of 70 per cent perchloric acid, in at least 1 hour.

The decrease in acidity of solutions of 70 per cent perchloric acid in acetonitril was explained by the hydrolysis of acetonitril to ammonium acetate, the reaction being catalyzed by perchloric acid; the acetate reacts basic to perchloric acid forming acetic acid and ammonium perchlorate. A corresponding cystin perchlorate solution is stable, the cystin perchlorate not catalyzing the hydrolysis.

Relation of the Parathyroid Glands to the Toxicity of Irradiated Ergosterol.—JAMES H. JONES (Department of Physiological Chemistry, University of Pennsylvania). Due to the similarity of the pathologic changes produced when either large doses of irradiated ergosterol or parathyroid extract are administered Taylor, Weld, Branion and Kay[1] have concluded that the toxicity of irradiated ergosterol is due to a stimulation of the parathyroid glands. If this conclusion is correct it should be possible to reduce the toxicity of irradiated ergosterol by removing

[1] The Canadian Medical Association Journal, 1931, **24**, 763; **25**, 20.

the parathyroid glands associated with the thyroid even though accessory parathyroid tissue remained intact. In the following experiments such studies have been conducted. The parathyroids were removed from rats but only those animals which were actually seen in tetany were used for the experiment. The daily dose of irradiated ergosterol necessary to cause death was no greater for the animals from which the parathyroids had been removed than for control animals which retained their complete parathyroid tissue. In like manner the time necessary for any given lethal dose to cause death was no greater for the operated animals than for the controls. Hypercalcemia was also produced as quickly and with as small amounts of irradiated ergosterol in parathyroidectomized animals as in normal unoperated animals. These data indicate that the toxicity of irradiated ergosterol is not due to stimulation of the parathyroid glands.

The Absorption of Glucose from Intestinal Loops.—I. S. RAVDIN, C. G. JOHNSTON and P. MORRISON (Laboratory of Research Surgery, University of Pennsylvania). Solutions of glucose in varying amounts, volumes and concentrations were introduced into jejunal loops prepared by the method by Johnston and the rate of glucose absorption was determined. It was found that with increasing concentrations, there was an increase in the amount of glucose absorbed. Variations in volume had a similar effect in that a marked increase in volume, concentration remaining constant, resulted in an increase in the amount of glucose absorbed.

When volume and concentration were so adjusted that the amounts of fluid removed after a 15-minute period were comparable, the amounts of glucose absorbed were similar when low concentrations were used (below 15 per cent), but were at considerable variance when wide differences (8 per cent to 55 per cent) in concentrations were used. In these experiments there was no relationship between the weight of the animal and the amount of glucose which was absorbed.

Poiseuille's Law and the Capillary Circulation.—EUGENE M. LANDIS (Laboratory of Zoöphysiology, University of Copenhagen). According to Poiseuille's law in the case of a homogeneous liquid flowing through a long tube of small diameter the volume, Q, of liquid which escapes in time, t, is given by the equation,

$$Q = \frac{\pi p r^4}{8 l \eta} \qquad (1)$$

where p is the fall of pressure in the tube, r the radius of the tube, l its length and η the coefficient of viscosity. The volume, Q, escaping from a capillary can also be expressed by the equation,

$$Q = \pi r^2 V t \qquad (2)$$

where V is the mean velocity per second. Substitution, rearrangement and changing the unit of pressure from dynes per square cm. to centimeters of water yields,

$$p = \frac{8 l \eta V}{980 r^2} \qquad (3)$$

The fall in pressure in cms. water can then be calculated for each capillary segment from the length in centimeters, viscosity in dyne seconds or poises per square centimeter, the mean velocity of flow in centimeters per second and the radius in centimeters.

A motion picture camera was used to record the flow of an opaque graphite suspension following blood through the capillary network of the frog's mesentery. The diameter, length and the mean rate of flow were determined for each vessel separately by studying the cinematographic film. The coëfficient of viscosity of frog's blood is usually given as 0.0253 and similar figures were obtained by viscosimeter in two observations. This value was used in computing the pressure fall since blood was being displaced from the capillary network while the observations were made.

When thus calculated from Poiseuille's law it appears that the total fall of pressure through the entire capillary network of the frog's mesentery cannot be less than 1.0 to 2.0 cm. of water. According to direct microinjection measurements of blood pressure in single capillaries of the frog's mesentery the average fall in pressure amounts to 4.3 cms. water.[1] The difference between the calculated and the observed figures indicates that the effective viscosity of blood in the capillary network is greater than the viscosity observed when blood flows through the relatively large capillary tubes of the ordinary viscosimeter. Additional evidence that this is the case was found in the literature. Therefore Poiseuille's equation cannot be applied to the capillary circulation except in the limited sense of indicating the lowest possible fall in pressure that can theoretically be associated with the observed rates of capillary blood flow. The true fall in pressure must apparently be determined by direct observations of capillary pressure.

[1] Landis, E. M: Am. J. Physiol., 1926, **75**, 548.

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